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A Correction.

Archives of Internal Medicine

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EXTRAMENINGEAL MENINGOCOCCUS INFECTIONS

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The meningeal picture resulting from meningococcus infection has so fixed the attention of clinicians and pathologists that the possibilities of extrameningeal infection by the organism have had scant notice. This has resulted in a general failure to recognize the fundamental nature of the disease as a meningococcus septicemia, which has in turn had important consequences in the fields of diagnosis and treatment.

The reason for this is not obscure. The premeningitic stage of the disease, which, up to the present, has been called epidemic cerebrospinal meningitis, is ordinarily not impressive enough to be of serious concern to the family physician, and is rarely, if ever, seen by the hospital physician or the consultant. Meningococcus infections apart from meningitis are practically unrecognized in civil life. The local meningeal involvement and the symptoms arising therefrom have been the criteria of diagnosis. To this the skill and care required to cause the organism to grow in artificial mediums is contributory.

In the receiving ward of a large military hospital acute disease is observed in its incipiency. The very hour the recruit in a well regulated camp is incapacitated from his severe routine, he is rushed to the base hospital where a specially trained staff awaits him. Under such conditions 315 cases of meningococcus infection were studied at Camp Jackson. In approximately 40 per cent. the diagnosis was made before meningitis developed. In 5 per cent. meningitis never developed at all. With few exceptions the earliest evidences of meningitis were preceded by symptoms of a general infection lasting from a few hours to several days, in exceptional instances, weeks. This initial stage of sepsis was repeatedly proved by blood culture, by clinical studies and necropsies. It has been sufficiently dwelt on in previous reports.[1] It is not our opinion, as one writer[2] has construed

1. Herrick, W. W.: The Epidemic of Meningitis at Camp Jackson, J. A. M. A. **70**:227 (Jan. 26) 1918. The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, Arch. Int. Med. **21**:54 (April) 1918. Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, J. A. M. A. **71**:612 (Aug. 24) 1918.

2. Neal, Josephine: Epidemic Meningitis, Med. Clin. North Am. **2**:223, 1918.

these reports, that epidemic cerebrospinal meningitis is a sepsis throughout its entire course. It is a blood stream invasion, a sepsis, at first, for a period averaging forty-eight hours, often more, at times less. Later there is the local process, usually in the meninges, not infrequently elsewhere.

Being revolutionary, this conception of the disease demands repeated emphasis. This emphasis is imperative because on it is based that modified therapy which, in proper hands, has mitigated the severity of the disease and greatly reduced the mortality — the intravenous serum treatment.

To emphasize the importance of the extrameningeal rôle of the meningococcus, both in the early stages of ordinary epidemic meningitis and in other less frequent conditions, the following cases are cited as types:

Case 1.—*Meningococcus Sepsis without Meningitis.* The patient, B. A., a private, 21 years old, was admitted to the hospital, Sept. 29, 1918, with a typical mild influenza. The temperature was 101 F., and there was moderate bronchitis, with headache, joint pain, coryza and cough. The temperature became normal October 3 and remained so. October 7, at 7:10 a. m., the emergency officer noted that the patient had a chill in the early part of the night, with pain in the chest which made him groan aloud. Perspiration covered the entire body. The pulse was weak and frequent; the temperature subnormal. There were signs of broncho-pneumonia at the bases of both lungs.

By 10 a. m. a petechial rash appeared. The spots rapidly increased in size and number, extending over the trunk, arms, face and conjunctivae. The patient quickly sank into coma. The general condition was very poor and the temperature was constantly subnormal. There were no specific signs of meningitis. The spinal fluid was water-clear, contained no globulin, showed sugar and 12 cells per cubic millimeter, but neither pus cells nor organisms. A note at that time recorded the opinion that the condition was meningococcus septicemia; prognosis, hopeless.

Despite this situation a trial of intravenous treatment was made and after the usual desensitization and administration of morphin and atropin the patient received 100 c.c. of antimeningococcus serum by vein. The patient made no response and died at 11:30 a. m., one-half hour after admission to the meningitis ward and only six or eight hours after the initial chill. Cultures from the heart blood and from the spinal fluid taken immediately on death showed meningococci. At death the body was a mass of purpuric blotches.

The body was embalmed shortly after death. The brain was removed by Paul Wegeforth, Captain, M. C., U. S. Army, on the following day. It was well fixed by the embalming fluid and showed no gross lesion. The remaining part of the body was not examined.

Microscopic Examination. — This was made by W. H. Norton, Captain, M. C., U. S. Army, Necropsy 18A137. Sections of the floor of the fourth ventricle, the left temporal lobe, the left frontal lobe, the wall of the lateral ventricle, the wall of the posterior horn of the left lateral ventricle, the left occipital lobe, the cerebellum and choroid plexus were all normal. There was no congestion, cellular increase or exudate.

Diagnosis.—Meningococcus sepsis.

Case 2.—*Meningococcus Sepsis.* The patient, a private, aged 21, was admitted to the X section of the base hospital late in the evening of Oct. 1, 1918, complaining of sore throat, general pains and weakness, all of which

had begun on the previous day. At 5:30 a. m., October 2, he complained of headache, increased weakness, pains in the back, legs and joints and sore throat. There was a petechial rash over the trunk, arms, legs and face. There were no definite meningeal signs or symptoms. At 7 p. m., October 2, he was apathetic, yet restless and was complaining of severe pain in all joints. His color was a combination of pallor and cyanosis, with a special cyanosis of the ears. The mouth was dry and coated. The heart and lungs showed nothing significant. The spleen was felt 1 inch below the costal margin. The neck was not stiff. There was tenderness and pain on manipulation of all joints with marked cutaneous hyperesthesia. There was no redness or swelling of the joints. The trunk, extremities, face and conjunctivae were covered with petechial spots, some three-fourths inch in diameter.

He was transferred to the meningitis ward as a case of meningococcus sepsis. All the deep reflexes were abolished. The joints were tender and painful on movement. General cutaneous hyperesthesia continued.

The patient died at 11:30 a. m., October 3. He had a subnormal temperature and an imperceptible pulse just before death. The blood cultures taken October 2 showed gram-negative diplococci giving the agglutination tests tabulated. For these I am indebted to Major Marshall A. Barber, S. C., U. S. Army, chief of the laboratory.

	Dilution				
	1:50	1:100	1:200	1:400	1:800
Rockefeller Institute antimeningococcus serum	++	++	++	+	+
New York City Health Department serum	++	++	+		
Mulford	+	+			
Lederle	++	++	+	+	
Type 1 serum	±				
Type 4 serum	++	+	Salt solution, negative		
Type 10 serum	+		Horse serum 1:50, negative		
Type 30 serum	±				
Type 60 serum	−				

Necropsy (18A136).—Necropsy performed at 9:30 a. m., Oct. 4, 1918, by P. Wegeforth, Captain, M. C. Private H. W. The body, seen just after death at 11:35 a. m., October 3, was that of a well developed man measuring 5 feet 8 inches. The skin of cheeks, eyelids, both arms, legs, body and shoulders was covered with large subcutaneous hemorrhages varying in size from a pinhead to a split pea. The petechiae on the upper arm were the most striking, and the largest. The outlines were irregular and presented no uniformity. Petechiae were present on the soft palate and both conjunctivae.

Head: The calvarium was easily removed and presented no abnormalities. The dura was normal in appearance, stripped easily from the bone and was lifted readily from the arachnoid. No petechiae were noted anywhere in the dura. The arachnoid was torn in places, but otherwise did not appear abnormal and no exudate could be noted beneath it, either over the hemisphere or base. The meningeal vessels over both hemispheres were apparently hyperemic in a slight degree, a condition which was not present over the base. No petechiae could be found on the leptomeninges. Sagittal section was made through the corpus callosum and the right lateral and third ventricles entered carefully. A very small amount of fluid was found in each, from which smears were made. The lateral ventricles appeaed normal. The choroid plexus appeared normal.

Lungs: No fluid was present in either pleural cavity The pleura over the bases of both lungs contained numerous petechiae of varying sizes, none larger than a split pea. Only a few scattered petechiae could be seen in the parietal layer, and they were located at the base. The organs themselves were normal. The bronchial lymph nodes were not enlarged.

Heart: The pericardium contained no excess of fluid. Within the membrane numerous petechiae were to be seen, especially in the visceral layer in the neighborhood of the apex and along each side of the coronary arteries. The parietal layer contained a few hemorrhages, but the number was small in comparison with those on the heart. The heart was normal in size. The endocardium and valves were normal, and no petechiae could be found in the cavity walls. The aorta was free of plaques.

Liver: Organ normal in appearance; no petechiae on its surface. On section the tissue had a slight yellowish cast in places.

Kidneys: Normal in size and appearance. On section no gross lesions were found. The pelves and ureters were normal; no petechiae in the capsules.

Pancreas: Normal.

Stomach and Intestines: No lesions found; no petechiae anywhere in peritoneum of intestines, mesentery or omentum.

Bladder: Wall in good condition; no petechiae noted in either external surface or in epithelium.

Prostate: Small, firm and on section showed no abnormality.

Bacteriology.—Blood Culture: Gram negative diplococcus with positive titer for meningococcus.

Ventricular Fluids: Postmortem smear negative for organisms.

Diagnosis.—Meningococcus bacteremia with hemorrhage into skin, throat, conjunctivae, pleura and pericardium.

Microscopic Examination.—By W. H. Norton, Captain, M. C., U. S. Army.

Lung: The alveolar walls are congested with erythrocytes and serum; the blood vessels dilated.

Heart: The heart muscle is normal. The pericardium is thickened by a surface coat of serum and fibrin and slightly raised by large collections of erythrocytes.

Liver: The liver cells are greatly shrunken, vacuolated and contain some brownish pigment. The interspaces throughout the lobules are dilated, principally by serum and fibrin. The process is more marked around the central veins.

Kidneys: The glomeruli are distended with blood, likewise the vessels. The tubular epithelium is broken up, and in many places all the nuclei have disappeared. There is considerable serum, fibrin and some infiltration with round cells between the tubules.

The spleen shows marked congestion, there being some phagocytic cells filled with pigment.

Prostate normal.

Central Nervous System: The lateral wall of the right lateral ventricle is normal. The floor of the fourth ventricle shows marked dilatation of the blood vessels with some serohemorrhagic exudate over the pia mater. There are a few round cells, but no polymorphonuclears.

At the base of the temporal lobe there is some hemorrhage and round cell infiltration between the pia and arachnoid.

The mesial surface of the parietal lobe shows hemorrhage and cellular infiltration of the pia and subarachnoid coats. While mostly mononuclears, there is here and there a polynuclear leukocyte. A like condition obtains over the cerebellum.

The choroid plexus shows extreme dilatation of the capillaries with small cysts filled with serous exudate, congestion and infiltration with leukocytes both mononuclear and polynuclear.

No collections of polymorphonuclear leukocytes are found on any of the surfaces examined.

Diagnosis: (1) acute serous meningitis; (2) congestion of the lung, liver, spleen and kidneys; (3) parenchymatous degeneration of liver and kidneys; (4) acute pericarditis.

CASE 3.—*Subacute Meningococcus Sepsis without Meningitis but with Other Local Symptoms.* The most striking case of this type was that of the head nurse in the meningitis ward. She was a very intelligent, vigorous and active woman of 28, who was particularly careful about infection, constantly wearing a mask while on duty and spraying two or three times a day with a solution of dichloramin-T or other antiseptics. In fact the thoroughness with which this nurse carried out all possible precautions was a subject of remark among her associates.

Jan. 16, 1918, there was an attack of tonsillitis with slight fever, headache and pain over the region of the right maxillary sinus. She gave up her ward duty and spent most of the following week in bed. About Jan. 23, 1918, there was found to be a sinusitis which was treated locally. Two days later an acute polyarthritis began. This involved hips, knees, ankles, elbows and wrists in rapid succession with moderate pain, stiffness, tenderness and slight swelling. The local symptoms, rather than the systemic disturbance forced the patient to remain in bed. After one week there was a slight improvement and the patient returned to duty, where she remained for several days, annoyed only by stiffness and soreness in the joints. About February 11, after being on duty seven days, an operation was performed on the maxillary and ethmoid sinuses which were drained with a trocar. No culture was made from these sinuses. Forty-eight hours after this surgical experience, there was a recurrence of the arthritis with severe local and general symptoms. There was a rapid loss of weight, recurring chills and irregular temperature and a general picture suggesting a septic arthritis. The patient rapidly became anemic, extremely weak, had moderate headache and exhibited a maculopapular eruption, not unlike that of typhoid fever. Full doses of sodium salicylate were given without effect.

A blood culture made February 16 by Major F. W. Baeslack, was positive for meningococci. At this time the temperature was ranging to 101 F., the pulse rate averaged 120 and the respirations from 24 to 30. There was no rigidity of the neck, no Kernig's sign, no headache or nausea, nothing suggesting meningeal irritation. February 16, 55 c.c. of antimeningococcus serum were given by vein. This was followed by a chill, but no other reaction. February 17, the temperature was 100. The only complaint was of painful joints. Sixty c.c. of serum were given by vein. On the 19th an intravenous injection of 70 c.c. was given. February 19 a general improvement was noted. Previously apathetic and distressed, she was now bright and resting very comfortably. The arthritis had lessened. February 20, 160 c.c. of serum were given intravenously. On this date the temperature was 102.4. February 21, there was a marked serum rash which lasted about five days. Blood culture made February 20 was negative. Convalescence was satisfactory, though somewhat prolonged by rather poor response to exercise on the part of the heart and a rapid heart rate. She returned to duty about April 1 and has since performed very active service in the hospital laboratory with no sequel whatever.

Lumbar puncture was not done because there was not the slightest clinical evidence of meningeal involvement, a possibility to which those in charge were naturally alert.

The notable change in the condition of the patient under specific serum therapy is important. From a very serious, progressive septic polyarthritis with advancing anemia, prostration and other attendant evidences of toxemia, within forty-eight hours the patient's condition changed, and in four days she seemed out of danger and made a recovery marred only by severe serum sickness.

Unfortunately, no culture was made from the accessory nasal sinuses at the time these were drained, nor were any nasopharyngeal cultures made except the routine three cultures just before discharge. These were negative.

CASE 4.—*Meningitis Tarda with Prolonged Stage of Meningococcus Sepsis. Meningitis a Late Development.* The patient, L. S., aged 24, a private, was admitted to the base hospital, Feb. 21, 1918. For the previous two or three weeks he had been troubled with frontal headache, at times so severe that he "could not see." Just previous to admission there had been chill and vomiting. On admission the temperature was 100 F., the pulse 62. He did not appear very ill. The tonsils were enlarged, ragged, but without exudate. There was a papular rash on the body.

The picture was so suggestive of an early meningitis that a lumbar puncture was done shortly after admission, Feb. 21, and 10 c.c. of perfectly clear fluid were removed. There was no increase in cells, no globulin and no bacteria.

February 26 there was a chill followed by fever and headache. The heart was negative. On the extremities and back there were a few tender, reddish spots, varying in size up to 1 inch in diameter and having the general appearance of an erythema multiforme. The patient was transferred to the rheumatism ward and given salicylates, which were without effect. March 9 there was a renewal of the headache. With this was no rigidity of the neck or abnormality of the reflexes. The left tonsil was ulcerated. The temperature was 103.6; the pulse, 98. On April 4, 1918, the temperature, after remaining normal two days, rose to 102.4. The throat and lungs were negative. Examination for malaria organisms was repeatedly negative. April 13 he complained of pain in the knees. These joints were slightly swollen, tender and hot.

During all this prolonged hospital stay, the patient was not very ill. It was difficult to keep him in bed and during the remissions in his symptoms he would get up and walk about the ward, often against orders. There was very little prostration, but he was dull, apathetic and his nutrition suffered. The temperature was extremely variable; remaining normal for a number of days, then rising to 103 or more. April 10, 1918, the patient was apathetic, the tongue was coated, the face cyanotic. The heart rate was slow and regular. The lungs were clear. The abdomen showed a slight tenderness in the right lower quadrant and right costovertebral angle. Skin spots, about one-fourth inch in diameter, rather bright red, disappearing on pressure, were present, for the most part on the abdomen, chest and back. These papules were much like the roseolae of typhoid, but larger. A blood culture was made. Infection of the right renal tract, atypical typhoid or a sepsis, either cryptogenic or arising from the tonsils, teeth or sinuses, were discussed as possibilities. April 17 the blood culture was reported positive for gram-negative diplococci. There were no signs of meningeal irritation. Many rose-colored spots continued to appear.

A diagnosis of meningococcus sepsis was made and active specific serum treatment begun. April 17, 110 c.c. of antimeningococcus serum were given intravenously. This was followed by chill and other signs of mild anaphylaxis. The following day the patient got out of bed, seemed better, received another intravenous injection and had a severe chill following it. In all, four intravenous injections of serum of 100 or 110 c.c. each, were given during four days, from April 17 to April 20, with subsidence of the temperature and some slight general improvement. April 25, a severe serum reaction followed. There were large patches of urticaria with swelling of the upper lip and of the ankles, and joint pain. April 28 the serum sickness was pronounced. On the following day there was a sudden change in the picture. Headache became intense and was not controlled even by morphin. Large purpuric spots appeared over the feet and legs. Forty-five c.c. of clear spinal fluid were removed under pressure. The cell count was 145. Globulin, pus cells and gram-negative diplococci were found. The patient rapidly developed the picture of a very severe cerebrospinal meningitis. After being in a critical condition for twenty-four hours he responded to vigorous intravenous and

intraspinal serum treatment and finally made recovery after a rather prolonged convalescence.

CASE 5.—*Local Extrameningeal Meningococcus Lesion in the Pleura without Meningitis.* The patient, S. R., aged 23, a private, was admitted to the base hospital, Camp Jackson, S. C., Nov. 17, 1917, complaining of a cold and pain in the chest, eyes and back. The temperature was 103; the pulse, 116. December 26 there was a vague eruption which was observed by the dermatologist, but on which no definite opinion was given. During the first week the temperature varied between 100 and 103. October 24 a bronchitis was discovered. November 28 a left pleurisy developed. On the following day a bronchopneumonia was discovered which subsided after a few days. Later this recurred and on December 4 signs of fluid were found at the base of the left chest. Exploratory puncture revealed a rather thick serous fluid of which 500 c.c. were aspirated. December 6 measles developed from which a very satisfactory convalescence was made until January 10, when there was a return of fever and pain in the left chest. January 14 an empyema was discovered. A left thoracotomy was performed by Major Meredith and the patient made a gradual but satisfactory recovery, being discharged from the hospital March 11. The purulent fluid aspirated from the chest January 14 showed a meningococcus of the regular type.

CASE 6.—*Local Meningococcus Infection of the Sinuses without Meningitis.* The patient, J. M. F., aged 25, a private, was admitted to the base hospital, Jan. 5, 1918, in serious condition, with cough, fever, coryza, cyanosis, tremor and prostration. There was rash which suggested fading measles. The lungs showed a bilateral bronchopneumonia; the temperature was 104.8 on admission and gradually fell, until at the time of death, January 12, it was 101. The pulse and respirations were constantly rapid. Extreme coryza was noted. At the necropsy on January 13 a bronchopneumonia was found. Examination of the accessory sinuses of the nose revealed abscess of the sphenoid and left frontal sinuses and the anterior and posterior ethmoid cells. Pus obtained from the sphenoid sinus contained a meningococcus of the regular type.

DISCUSSION

Cases of which 1 and 2 are types are of great and tragic interest. Of these, some ten have been studied. They present the features of *purpura fulminans* — a sudden onset with chill, moderate or high fever, great prostration, restlessness with apathy, deepening into stupor or coma, which endures until death. The pulse is rapid, running, of small volume, weak and of low pressure. The color is a cyanotic pallor that is a mask of death. The rash begins as purple blotches on the trunk or elsewhere. These increase in size with incredible rapidity until coalescent areas may transform a considerable area of the body surface — even one-third — by ominous purple patches, continually extending until the fatal issue. In addition to the diffuse purpura, punctate petechial spots are thickly sprinkled over trunk, face, extremities and mucosa of the mouth and eyes and seem an independent lesion. No other infection so quickly slays. A nurse did full duty all one morning, felt ill at noon and was persuaded to leave her ward. Twenty hours later she was dead, the skin surface a mass of purpuric splotches. A soldier suffering mild symptoms at

4 p. m., walked into the ward carrying a suit case and not seeming very ill. At 8 p. m. he was dead; the body surface well covered with purpura. Cases of this type have no meningitis either clinically or at necropsy. The spinal fluid is negative and death is the result of the overwhelming sepsis. The blood culture is practically always positive.

In Case 2 the meninges showed a reaction not greater than that observed in the pericardium and not as great as that at times found in those dead from acute infections other than that under discussion. Congestion and increase in mononuclear cells are noted, with a few polynuclears in certain areas, but no free exudate on any of the surfaces. Doubtless here is the very earliest step in a meningitis which would have developed within a few hours into the picture of a local polymorphonuclear preponderance with organisms. Certain is it that at the end of four days' illness the lesions characteristic of epidemic meningitis had not developed, and that death resulted from the general systemic invasion and not from the slight local reaction in the meninges.

In Case 1 death was due entirely to the meningococcemia, there being no indication of meningitis even on microscopic examination of sections from the central nervous system.

In the mind of one who has repeatedly witnessed this picture comes the question if many of the instances of purpura fulminans are not examples of this kind of meningococcus infection. The failure to secure positive bacterial findings in cases of this character heretofore may possibly be explained by the difficulty met in cultivating the meningococcus by the conventional methods. The importance of following such successful technic as that described by Baeslack and his associates[3] in the study of the blood of all fulminating purpuras of which the etiology is obscure is emphasized.

Instances of which Case 3 is a type are doubtless rare. It is certain that they are rarely recognized by ordinary laboratory or clinical methods. That the *Diplococcus intracellularis* can cause an acute polyarthritis of a serious septic variety without meningitis has, to our knowledge, not been recognized. Arthritis is a fairly common complication of epidemic meningitis and was observed in about 10 per cent. of our cases. Its occurrence apart from meningitis is but another link in the quite complete chain of evidence establishing the blood stream as the route of meningococcus invasions.

The practical point brought out by this case is that all instances of acute or subacute septic arthritis of which the etiology is obscure should have the benefit of the suspicion of a meningococcemia and

3. Baeslack, F. W., Bunce, A. H., Brunelle, G. C., Flemming, J. S., Klugh, G. F., McLean, F. H., Solomon, A. V.: Cultivation of the Meningococcus, Intracellularis from the Blood, J. A. M. A. **70**:684, 1918.

the trial of appropriate blood culture methods. The importance of proper diagnosis is apparent in the very satisfactory response to intravenous serum treatment.

Case 4 is a remarkable example of *meningitis tarda* as recently described by French observers (Santon,[4] Aime[5]). In these cases the symptoms of a systemic invasion of the meningococcus precede by many weeks the final meningeal localization. The features of this long prodromal or premeningitic period are irregular temperature, chills at infrequent and irregular intervals, joint pains, headache, relatively slight prostration, high leukocytosis and polynuclear percentage, tonsillitis and a certain hebetude that characterizes all meningococcus infections. It is probable that some of these cases never develop the secondary meningitis and go on to recovery or fatal issue without recognition (*vide* Case 3). That this case should develop meningitis one week after intravenous treatment for the sepsis may be explained as analogous to the relapsing cases of meningitis. Such relapses are probably from a focus that has not been reached by the earlier course of treatment. The coincidence of this second outbreak with serum sickness corroborates a general impression that the meningococcus thrives in soil prepared by any agent lowering resistance. Santon[4] describes a case in which meningococcemia dated from May 6, but meningitis did not develop until July 14.

While there is no proof, it is possible that the infection for which the patient, Case 5, entered the hospital and which lasted from November 17 to December 6, when measles developed, was an atypical type of meningococcemia. The irregular temperature, the rapid pulse, the atypical rash with which the staff was not at that time familiar, may possibly be ascribed to this cause. The finding of the meningococcus in the pleural fluid has not been duplicated in this hospital. Captain H. T. Chickering has, however, recovered the meningococcus by lung puncture in a case of bronchopneumonia following measles. This case showed no meningeal symptoms and made recovery.

Pneumonia and pleurisy are common in meningococcus infection both as precursors and as complications of onset or of the later course. A separate report of the pulmonary features of meningococcus infections is in preparation and has been specially studied with First Lieutenant J. Stern, M. C.

The finding of meningococci in the sphenoid and ethmoid sinuses as in Case 6 is not unexpected. Cleminson[6] remarks that study points to the accessory sinuses as being the main seat of meningococcus

4. Santon: Meningococcemia, Paris méd. **8**:86, 1918.

5. Aime, H., and Chene, H.: Parameningococcus Septicemia, Paris méd. **8**:118, 1918; Abstr., J. A. M. A. **70**:1125 (April 13) 1918.

6. Cleminson, F. J.: Nasopharyngeal Conditions in Meningococcus Carriers, Brit. M. J. **2**:51 (July 20) 1918.

infection in carriers. In about 90 per cent. of a series of necropsies on fatal cases of measles in the Base Hospital, Camp Jackson, examination of the accessory sinuses revealed the quite unexpected occurrence of empyema. The meningococcus was found but twice in the pus from this source. Neither patient had history of meningitis.

To call a disease with the wide range of possibilities of infection of joints, pericardium or other body structures epidemic cerebrospinal meningitis is incorrect and misleading. The term epidemic should be abandoned, as there is no difference between the epidemic and sporadic forms. We might as well speak of epidemic measles or epidemic scarlet fever. The cerebrospinal distribution of the disease is not specific, as infections from the other micro-organisms — tubercle bacilli, *Spirocheta pallida* — have the same localization. Hence we should drop this term cerebrospinal.

The change in nomenclature suggested by Heiman and Felstein[7] should be generally adopted. As a general term, meningococcus infection should be used. To denote the local processes, meningococcus meningitis arthritis, etc., are brief and satisfactory.

Let us hereafter speak of meningococcus meningitis when dealing with meningococcus infection with predominant cerebrospinal symptoms.

CONCLUSIONS

To emphasize the extrameningeal rôle of the meningococcus, 6 cases are reported in which meningitis was absent or a subordinate part of the disease process. These cases are:

1. Meningococcus sepsis without meningitis either clinically or at necropsy.

2. Meningococcus sepsis without clinical meningitis: at necropsy, meningeal congestion and arachnoid cell hyperplasia — the earliest stages of meningitis.

3. Meningococcus sepsis without meningitis; septic polyarthritis; recovery with intravenous treatment.

4. Meningitis tarda, or meningitis with premeningitic stage of meningococcemia of several weeks' duration.

5. Meningococcus pleurisy, and, 6, meningococcus empyema of accessory nasal sinuses, both without meningitis.

The term epidemic cerebrospinal meningitis should be abandoned.

The term meningococcus infection should be used to denote such general processes as meningococcus sepsis. Meningococcus meningitis should be the term used in the case of meningococcus infection with predominant cerebrospinal symptoms.

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7. Heiman, H., and Feldstein, S.: Meningococcus Meningitis, J. B. Lippincott Company, Phila., 1913.

CLINICAL STUDIES ON THE EFFECTS OF LOUSE BITES—PEDICULUS CORPORIS *

ARTHUR D. HIRSCHFELDER, M.D., AND WILLIAM MOORE, A.B.
MINNEAPOLIS

The previously reported observations of one of us (M.)[1] indicated that a macular erythematous skin eruption, somewhat resembling that of measles or German measles, distributed over the chest, back and abdomen, may occur in a normal person who allows lice to feed on the skin of his forearm only. This eruption was accompanied by general lassitude and malaise, headaches, and peculiar pains in the calves of the legs and soles of the feet, particularly under the toes. Unfortunately the association of these symptoms with louse bites was not at first noted, hence definite data of the illness are not available.

REVIEW OF LITERATURE

An examination of the literature shows that phthirus pubis may cause a rise in temperature (Payne[2]) due to the toxic action of its bites, while it has also been demonstrated experimently to be the cause of maculae caeruleae. Duguet[3] has shown that these spots may also be produced by the inoculation of that portion of the body of the louse in which the salivary glands are located. A number of references appear in the literature to rashes caused by the bites of *Pediculus corporis,* but these are not similar to the rash encountered in our experiments. Prurigo, prurigo senilis, urticaria, and porrigo are grouped together by the editor of the *British Medical Journal* (1869) under the title Pedicularia.[4] More recently, Peacock (1916) refers to "louse rash" as being distressfully common among British troops,

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* A research undertaken for the Medical Division, National Research Council.

1. Moore, W.: An Interesting Reaction to Louse Bites, J. A. M. A. **71**:1481 (Nov. 2) 1918.

2. Payne, J. F.: Maculae caeruleae and Other Symptoms Produced by Pediculi pubis, Brit. J. Dermat. **2**:209, 1890.

3. The New York Medical Journal in an editorial dealing with fatal pediculosis (July 29, 1905, p 234) mentions a worker, Briguet, as offering experimental evidence to show that these macules are due to a toxin secreted by the insects. The work of Briguet cannot be traced, and it is possible that the reference is to the work of Duguet: Sur les taches bleues: leur production artificiele et leur valeur semeiologique, Ann. de dermat. et de Syph. **10**:545, 1880. Cited from Nuttall, Parasitology **10**:378, 1918. Ibid.: Les taches bleues et le pou de pubis, Compt. rend Soc. de biol., April 17, 1880; Experiences et recherches nouvelles sur les taches bleues, Ibid. 1882, p. 617.

4. Editorial: Pedicularia, Brit. M. J. **2**:612, 1869.

but the reference appears to refer to cases of urticaria. In our experiments, although urticaria appeared where the lice were fed (in the cases of S. A. G. and W. G.), the rash encountered on the other portions of the body was quite distinct and could not be classed as a pedicularia. Only in one case (W. M.) was a slight melanodermia present in the area where the lice fed.

Jamieson (1888)[5] records two clinical observations of young persons infested with lice with a temperature of 103 F. in the one case and 106.2 and 106.4 F. in the other case, which returned to normal after the patient was bathed and freed from lice. After reviewing the literature dealing with the toxic effects of louse bites, Nuttall (1918)[6] sums up as follows: "Apart from the maculae, phthirus, like P. humanus, fleas and mosquitoes, may cause a febrile condition owing to skin irritation, although this appears to be rare; with the removal of the lice, the fever promptly subsides." No mention, as far as can be discovered in the literature, is made of a rash similar to that encountered in our experiments.

EXPERIMENTAL

The present series of observations was undertaken at the suggestion of Prof. Richard M. Pearce, chairman of the Division of Medical and Related Sciences, National Research Council, in order to determine whether the previously recorded observations represented a peculiarity of the individual on whom the lice had fed, or whether it might be regarded as a general phenomenon. There naturally arose the question as to whether the condition represented sporadic typhus fever, trench fever, or some other infection, on the one hand, or a reaction to toxic products derived from the louse. Such a reaction might represent either a primary intoxication or a state of anaphylaxis. In view of the fact that one of the individuals tested had never been bitten by lice before, the rôle of anaphylaxis seems unlikely.

Four perfectly healthy young men, members of the Faculty of the Department of Agriculture of the University of Minnesota, volunteered for the experiments. They were examined by one of us (H) and found to be normal, except in some cases for the enlargement of a lymph gland here and there. The total blood counts, hemoglobin, lymphocytes and differential counts were taken, and the two latter were repeated daily or at frequent intervals. The Wassermann reaction was taken and found by Prof. W. P. Larson to be negative in each case.

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5. Jamieson, W. A.: On Some Rarer Effects of Pediculi, Brit. J. Dermat. **1**:321, 1888.

6. Nuttall, G. H. F.: The Pathological Effects of Phthirus Pubis, Parasitology **10**:375, 1918.

Each of the subjects allowed himself to be bitten twice daily by the number of lice specified. These lice were raised from eggs and had never fed on any except healthy members of the faculty of the University of Minnesota, who volunteered for the work. According to the work of Strong[7] and his collaborators, and Byam[8] and his collaborators, therefore, these lice could not be carriers of trench fever.

In every individual bitten, except W. M., there was a prompt rise of temperature ranging from 99.3 to 99.9, after the lice had been fed. Sometimes, as in the case of S. A. G., this occurred with surprising rapidity and the temperature reached 99.6 within an hour after feeding. In every case the afternoon temperature on the first day, six or seven hours after the first feeding, was well above normal and within from one to four days a well defined enlargement of the lymph glands of the axilla was noted. These glands, as well as the inguinal and submaxillary glands which also became enlarged, were quite tender in two of the individuals (S. A. G. and W. G.).

Except in the case of W. M., who must be considered to have developed a certain degree of immunity to the bites, having fed lice off and one for over a year, it required from three to eight days for this swelling of the glands to disappear and from four to ten days for the temperature to return to normal. September 27, S. A. G. and W. G., whose condition was then normal, started on a canoe trip. During the trip S. A. G. noted that his temperature had again risen, but having no thermometer the exact temperature is not known. Immediately on his return at 7.30 p. m., September 30, the temperature was taken and found to be 102.7 F. It was noted that all the lymphatic glands previously affected were again enlarged. His temperature remained at from 100 to 101.7 F. for five days after his return, while the swelling of the glands gradually subsided. W. G., who had not fed so many lice nor for so long a period, was not appreciably affected.

In three out of four of the subjects a well defined rash composed of semilunar and crescentic macules from 2 to 3 mm. in size resembling those of a fading measles or German measles occurred. The rash was not very striking and yet was definite enough to be seen without difficulty when it was at its height. The macules disappeared on pressure. It was distributed over the chest, back and upper abdomen, and in no case appeared on the face, neck, arms or lower

7. Strong, Major R. P., and Others: Report on Progress of Trench Fever Investigation, J. A. M. A. **70**:1597, 1918.

8. Byam, Major W., and Others: Trench Fever: A Report of Clinical Observations and Research as to the Etiology, Pathology, Prophylaxis and Treatment of Trench Fever Among Troops, J. A. M. A. **71**:21, 110 and 188, 1918.

limbs. It was always most distinct and persisted longest in the regions between the nipples and the lower costal margins.

In none of the individuals was the spleen palpable, nor was its outline determined by both light and auscultatory percussion sufficiently enlarged to be definite. None of the persons, including Moore himself who was one of the subjects, suffered from the peculiar pains or sensations in feet and legs which had been described by Moore[1] in his previous attacks.

The blood cultures, aerobic and anaerobic, taken by Prof. W. P. Larson when the fever was at its height, were negative.

Three c.c. of the blood of one of the subjects (S. A. G.) was injected subcutaneously under the arm of another individual (R. A. G.). He experienced, within forty-eight hours, a definite rise in temperature to 99.5 and suffered headache and mild sore throat, and diffuse small râles were present in his chest; but this was probably due to an epidemic of "colds" which was rife at the time, rather than distinctly due to anything traceable directly or indirectly to the louse. The following day his temperature was normal and remained below 99 F. for the following two weeks while under observation. This phase of the subject, however, warrants further investigation.

The fact that the condition was transmitted by lice which had never bitten diseased individuals, and that no opportunities existed for inoculation with the feces of the louse, since immediately after feeding, the arm was carefully bathed with alcohol and in some cases treated with ammonia and glycerin, as well as the negative character of the blood culture, point against either typhus or "trench fever." The absence of both positive blood culture, leukocytosis and increase in polymorphonuclear leukocytes, as well as the absence of any foci of pyogenic infection at the site where the lice fed, rule out simple pyogenic infection.

The fact that two of the subjects who had definite papular eruptions at the site of feeding had also fed lice for a certain period of time a year before, while the one person (J. J. W.) who had never fed lice before had no skin eruptions whatever, raises once more the question of anaphylaxis as a possible contributory factor in part of the syndrome. That anaphylaxis was not the only factor, however, is proved by the fact that he, too, had fever and glandular enlargement just as did the others.

While we cannot regard it as proved conclusively, the results of the foregoing observations point more strongly toward the presence of a substance in the louse sufficiently toxic to give rise to a generalized skin eruption and mild fever. This may or may not be protein in nature. The absence of any regularly occurring wheal or similar

lesion at the site of the feeding demonstrates that it probably is not a local irritant like those inserted by bees and mosquitoes, and it is probably not one of the lower organic acids.

The subject must be investigated further before any conclusions regarding this can be drawn.

On the other hand, it was quite clear that for the general health of the individual the bites of lice, even when "home grown," is not an indifferent matter, but greatly impairs his health and bodily vigor. In three of the individuals it was found, as might have been expected, that even relatively mild exercise such as an hour's walk or a morning working in the garden caused the temperature to rise up to 99.8 or 100.6 F. at times when it had been remaining below normal; while in one case more strenuous exercise after apparent recovery caused the temperature to soar to 102.7 F. with swelling of the glands. Accompanying these conditions in all cases a feeling of feverishness and weakness was experienced. The bodily vigor of all these individuals living in their normal excellent environment was therefore much impaired. Had they been living the life of soldiers, their bodily efficiency would surely have been impaired to a much greater extent. If it should appear from subsequent experiment that second and later infections with lice give greater response than first infections, this would only serve to enhance the importance of the question from a military standpoint. From any standpoint, whatever, it becomes obvious, as a result of these experiments, that men who are subject to louse bites have a lower mental and bodily vigor, and that, other things being equal, a louse-free army would be considerably better fighting men than the same army louse-infested.

CLINICAL OBSERVATIONS

CASE 1.—Aug. 27, 1918. W. M., associate professor of Entomology, University of Minnesota; aged 31; married.

Family History.—Father died at 70 with acute Bright's disease. Mother died of apoplexy at 65. The patient had eight brothers and sisters; all died of scarlet fever in childhood, except one sister, who died of Bright's disease at 45, and another sister still living and well. No members of the family have had skin disease, but all three of his children have eczema, which the patient says is inherited from their maternal ancestors.

Personal History.—Scarlet fever at 2½; no kidney trouble, no sequelae; measles at 12; chickenpox at 17; blood poisoning at 24, following a splinter in the finger; no other complications or skin eruptions. This took place while patient was in South Africa, where he remained for three and a half years and was well otherwise. He returned to this country five years ago. At 27 he had grip, followed by inflammation of the right kidney (Dr. E. K. Green and F. S. Bissell). He had some pus in the urine. This was regarded as secondary to the grip. At 30 he had grip again, and then developed an infection in the left antrum which was repeatedly punctured. At 31 he had an infected tooth removed and also tonsils removed. Since then has been well, except for the present illness. No venereal illness.

Present Illness.—He was perfectly well until the first week of May, 1918, when he began to feed 700 to 800 lice twice daily. On May 7, he began to have malaise, headache and indefinite pains all over the body. A rash similar to that of German measles soon developed and was especially marked over the shoulders and abdomen (German measles was prevalent in the community at the time). He thinks that he had a mild fever. This lasted about three days. He returned to normal and resumed the feeding of the lice. He had no further symptoms until May 28, when an attack similar to the first one developed, with a temperature rising to 102 F.

No glandular enlargement was found during this attack, nor was any enlargement of the spleen noted (A. D. H.).

The patient says that the onset of attacks of this illness was gradual; beginning with a general tired feeling, particularly noticeable in the calves of legs and down the shin bone and underneath the soles of the feet, particularly in the phalangeal region, but not specially on moving the joints. It was worse after going to bed—severe enough to keep him awake. This continued a week or more before he became sick and before he noticed the onset of the fever. About the same time he noticed a dull feeling in the head which developed into a definite headache at the height of the disease.

He was never nauseated; but lost appetite for about two days at the fastigium; never vomited; no nosebleed.

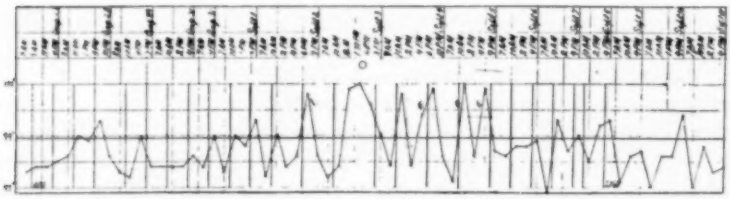

Chart 1.—Rectal temperature curve of W. M. Vertical lines represent louse feedings; the number of lice given at start and finish; O represents occurrence of rash, and E when exercise was taken.

At the fastigium he had pains in the joints, worse on moving them, but the joints were never swollen or tender on touching or on pressure.

The urine was neither much increased nor decreased; nor did he have to void at night more than usual. Apart from a little local erythema lasting only during time the patch is worn, the patient has had no eruption at the site where patches of louse killing substances have been worn.

Physical Examination.—The patient is a tall, well nourished individual, of good, though rather sallow color. The gums and mucous membranes are of good color; sclerae clear; no glandular enlargement present anywhere; tonsils absent; pharynx slightly reddened Thyroid normal; no tracheal tug. Lungs clear on auscultation and percussion.

Heart dulness extends 4.5 cm. to right of midline and 9 cm. to the left. Sounds clear. Blood pressure 110-80; pulse rate 64; arteries not sclerotic. Abdomen negative. Liver reaches to the costal margin in mammillary line; not palpable. Spleen not palpable. Dulness 8 by 4 cm. No areas of spasm, rigidity or tenderness. Shins clear; joints normal; no tenderness anywhere in joints or muscles, though patient complains of a tired feeling in the calves of both legs in the last couple of days.

Over the anterior surface of the left forearm where the lice are fed there is a very faint macular eruption somewhat resembling measles in its appearance. The spots disappear on pressure. About the bend of the elbow, this

is absent and it is absent from the right arm, which is not used for feeding. This eruption is fainter, but otherwise similar to the eruption present at the height of the febrile illness mentioned in the history. The Wassermann reaction is negative.

Blood Count: Red blood cells 4,400,000; hemoglobin 80 per cent.; leukocytes 7,100; polymorphonuclears 70 per cent.; lymphocytes 22 per cent.; large mononuclears 3 per cent.; transitionals 1 per cent.; eosinophils 4 per cent. Urine clear, straw colored, acid; specific gravity 1.016; no albumin, no sugar; a few epithelial cells present.

Sept. 3, 1918. For the previous three days the patient has had more or less biparietal and vertical headache, as well as a sort of dazed or confused sensation in the head, and a general tired feeling in the legs from the knee down; no definite pains in the feet. He has not been sleeping well. Chart 1 shows the temperature record. At present the temperature is 99.8 F. (rectal); pulse rate regular, 72. Blood pressure, maximal 122; minimal 90; heart not enlarged; sounds clear. The spleen is not palpable and does not reach the costal margin; dulness 10 by 4 cm. Liver not palpable. Glands not enlarged.

Over the lower part of the chest in front and between the shoulders and over the area of the insertion of the diaphragm there is a very faint macular erythema similar in appearance to that present over the anterior surface of the left forearm. Over the right forearm none is visible.

Blood count, September 4, leukocytes 6,700; polymorphonuclears 68 per cent.; lymphocytes 28 per cent.; large mononuclears 3 per cent.; transitionals 1 per cent.; no eosinophils seen in 100 cells counted.

Case 2.—S. A. G., assistant in Entomology, University of Minnesota; aged 27; unmarried.

Family History.—Father and mother living and well. Three sisters and two brothers all alive and well.

Personal History.—Measles, chickenpox and whooping cough as a child; no scarlet fever or diphtheria or typhoid fever; rheumatism uncertain. As a child the patient was jaundiced and his digestion was easily upset. He is subject to mild tonsillitis and grip and light colds in the winter; but no other illnesses. Does not have asthma, but has had eczema on eye and thumbs both summer and winter, for which he has been treated by Dr. Franklin Wright. No hives or angioneurotic edema. He is not susceptible to poisoning by poison oak. In the winter of 1918 he had an abscess in the left groin, which came without apparent cause, and was opened. There is no history of venereal diseases.

The patient fed the lice used in this series of experiments for about four months in 1917. During the first month, there was no sign; then a red papular eruption would appear at the site of feeding, appearing immediately after feding and lasting throughout the months in which feeding continued. After he stopped feeding them, it subsided within a week.

The patient began feeding the lice Sept. 9, 1918, at 9:30 a. m., at which time his skin was perfectly clear. Feeding lasted about half an hour and when the lice were removed his arm was covered with the red papular eruption mentioned later.

The temperature (rectal) taken yesterday (September 8) was from 98.1 F. to 99, but now (September 9) has gone to 99.8 at 1 p. m. At 10 a. m. (September 11) it was 99.6 just after feeding the lice, but today (September 10) at 7 a. m. it was 98.4. He has no headache, and does not feel chilly or hot, and does not feel quite as strong as normal. No pains in legs or other peculiar feelings.

Physical Examination.—This shows a well nourished man of good color; pupils equal and react to light and accommodation; color good; tongue clean; throat not reddened. Thyroid not enlarged; no eye signs of exophthalmic goiter (Basedow's disease).

There is no general glandular enlargement, but the left inguinal glands are slightly enlarged. Thorax well formed, symmetrical; lungs clear on auscultation and percussion. Heart not enlarged; extends 4.5 cm. to right; 10 cm. to left. There is a soft systolic murmur over the apex, not transmitted; no murmurs over the base. Blood pressure, maximal 110, minimal 80; pulse rate 104. (Patient says that he usually has a rapid pulse.)

Abdomen negative, liver and spleen not enlarged or palpable; splenic dulness 8 by 4 cm. No rigidity or tenderness.

Skin: In the left inguinal region there is a scar of the abscess previously mentioned. No areas of eczema are now visible.

Over the left leg there is a group of large scars due to an old compound fracture. The right shin and leg are clear, as are also the chest, back, abdomen and right forearm.

Over the entire anterior surface of the left forearm there is an irregular, red, macular and maculopapular eruption which is not infiltrated or hemorrhagic. The red color disappears on pressure. The blotches vary from 2 mm. to 5 cm. in diameter. This eruption corresponds sharply to the areas where the lice feed.

Urine, straw colored; specific gravity 1.020; no albumin; no sugar; many leukocytes.

Blood culture negative. Wassermann reaction negative. Red blood cells 4,272,000; hemoglobin 83 per cent.; leukocytes 7,450; polymorphonuclears 69 per cent.; lymphocytes 30 per cent.; large mononuclears 1 per cent.; no eosinophils (100 cells counted).

Sept. 10, 1918. The patient is quite normal today; temperature normal; feels better than yesterday. The skin eruption has begun to subside and is now more copper-colored and the papules are less raised. This is in spite of the fact that he has fed about 2,000 lice once today and twice yesterday. There is no glandular enlargement. The soft systolic murmur noted yesterday is still present today, but not transmitted beyond the apex. The pulse rate is 92. The spleen is not enlarged and not palpable.

Sept. 12, 1918. Heart sounds as before; no further enlargement of heart, liver, spleen or glands. The eruption on the left forearm has now become confluent, somewhat infiltrated throughout, and the papules are slightly higher than before. The patient now complains of pain along the inner surface of the upper arm 6 cm. above the elbow near the course of the brachial vein, where a small lymphatic nodule less than 5 mm. in size can be felt. The epitrochlear lymph gland is not palpable, nor is the brachial vein. Leukocytes 9,180; polymorphonuclears 89 per cent.; lymphocytes 11 per cent.

Sept. 14, 1918. The patient does not feel well today. Yesterday the temperature was 100.4 and he did not feel steady on his feet, but he had no headache or other symptoms. Today he feels a little weak.

The rash on his left arm is still present and about as before, except that the infiltration has diminished a little in intensity. The induration felt near the course of the brachial vein has subsided, as has also the tenderness in this region.

Over the chest there is present the faintest, just discernible eruption in discrete and confluent faintly pink macules from 2 to 5 mm. in diameter. These become pale on pressure. This is not present over the right arm. It is barely distinguishable over the back; not at all over the abdomen or elsewhere on the arms.

The epitrochlear glands and posterior cervical lymph glands are not palpable, but the left axillary glands are enlarged and tender. The submaxillary glands are enlarged and quite hard on both sides and the glands in both inguinal regions are definitely enlarged.

The spleen is not palpable and its dulness covers the same area as before.

The heart has not changed. Leukocytes 6,150.

Sept. 15, 1918. Yesterday morning, just after the examination, the patient began to feel pains on the medial side of left arm just above the bend of the elbow and extending up about half way to the axilla. Last night he was awakened during the night by pain under the axilla. Occasionally this extended down the left axillary region. There was no headache or pain in shins or feet. Today he still feels this pain and feels rather weak.

Today there is definite scaling over the area of eruption on the left arm, the infiltration of which is somewhat harder than before, but the area appears less edematous and is somewhat shrunken.

The epitrochlear glands are not palpable, but the left axillary and anterior cervical glands and the right axillary and the submaxillary lymphatic glands are palpable and sore, and the left posterior cervical and axillary glands are enlarged and palpable. The spleen is not palpable but the area of dulness seems slightly enlarged—9.5 by 5 cm.

Temperature is now 99.8 and pulse rate 90. The heart area and sounds are unchanged.

There is a just discernible maculation of discrete macules (from 2 to 3 mm.) over chest and back and especially over the abdomen. Though visible to several of the observers, it would not be sufficient to attract attention of a casual observer. Three c.c. of blood from the median basilic vein were injected under the skin of R. A. G.

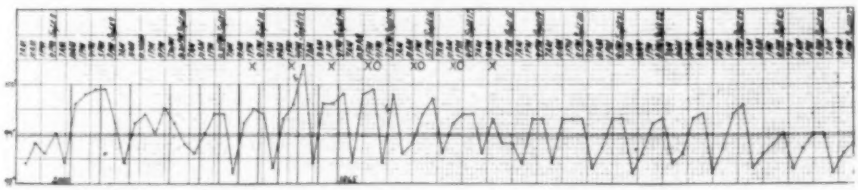

Chart 2.—Rectal temperature curve of S. A. G. Markings same as in Chart 1, with X representing swelling of glands.

Sept. 16, 1918. The rash has faded over the chest and the forearm eruption is gradually drying up. The lymphatic glands are still tender and enlarged, though somewhat less so than yesterday.

The patient took a walk yesterday afternoon. Before the walk the temperature (at 4 p. m.) was 98.4. He walked 4 miles, ate supper and then took his temperature at 7:30 p. m., when it was 99.8. At that time he felt tired and not as strong as usual.

Spleen not palpable—8 by 4 cm. Pharynx slightly reddened.

Sept. 17, 1918. The patient feels a little better. The temperature has not gone above 99.4. The glands are still somewhat tender, but less so than yesterday. The erythema has diminished to the point of being barely visible. Leukocytes 7,450; polymorphonuclears 61 per cent.; lymphocytes 33 per cent.; large mononuclears 3 per cent.; eosinophils 3 per cent.

Sept. 18, 1918. Feels well again; rash has faded. Temperature 98.8 at 1 p. m.; 99.3, however, at 11 a. m. The glands have diminished in size and soreness, but still are a little sore. The spleen is not palpable. The rash on the arm is drying up. The pharynx and pillars of the fauces are slightly injected. This is, however, often present with the patient under normal circumstances. Leukocytes 7,500.

Case 3.—W. G., engineering student, aged 19; unmarried. (Brother of S. A. G.)

Personal History.—The patient had had measles, chickenpox and mumps as a child; diphtheria at 6; no scarlet fever or rheumatism; no skin diseases

or asthma; occasional attacks of tonsillitis, for which the tonsils were removed four years previously. At the same time adenoids were removed. Varicose veins were removed two years prior to the experiments.

Physical Examination.—(Sept. 12, 1918.) A well nourished young man of good color. Pupils are equal and react to light and accommodation. No eye signs of exophthalmic goiter (Basedow's disease). Thyroid gland just palpable; no general glandular enlargements, but the right epitrochlear and both inguinal glands are enlarged and palpable.

Blood Count Sept. 12, 1918. Red blood cells 4,256,000; hemoglobin 84 per cent.; leukocytes 9,250; polymorphonuclears 75 per cent.; lymphocytes 17 per cent.; large mononuclears 5 per cent.; transitionals 0; eosinophils 3 per cent.

Urine straw colored, acid; specific gravity 1.028; no albumin, no sugar; ten leukocytes seen in specimen examined; Wassermann reaction negative.

Sept. 13, 1918. This morning the patient's temperature was 98.1. At 9 a. m. he fed the lice for fifteen or twenty minutes and at 10 a. m. the temperature was 99.1. At 1 p. m. it was again 98.6. When seen at 2:15 p. m. the skin of his left arm was normal; over the chest, especially below the level of the nipples, there was a very faint, just discernible patchy erythema in patches from 0.5 to 1 cm. in area of the measles type, which was not discernible yesterday.

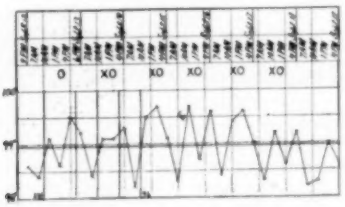

Chart 3.—Rectal temperature curve of W. G. Markings same as in Charts 1 and 2.

The dermatographia seems a little more marked than yesterday but does not bring out the rash mentioned either along its borders or in its vicinity. The spleen and glands are as before.

Sept. 14, 1918. The rash seems more definite today, but is still not definite enough to attract attention. Its presence was confirmed by several independent observers. Leukocytes 9,250. The right epitrochlear gland is still palpable, as are also now the axillary and inguinal glands and the submaxillaries. The spleen is not enlarged.

The area of the forearm corresponding to last night's feeding now shows numerous red infiltrated papules about 3 mm. in diameter. The area of this morning's feeding shows nothing.

Sept. 15, 1918. The rash is about the same as yesterday. The right epitrochlear gland and the axillaries and inguinals are still palpable. Spleen not enlarged; area of dulness 8.5 by 4.5. The erythema is about as before.

Sept. 16, 1918. The patient dug potatoes all morning. At noon he felt some malaise and less well than before. He had headache and felt tired, weak and sick, but there was no nausea or vomiting.

The eruption was still just discernible. The lymph glands were still enlarged and tender. Leukocytes 8,450.

Sept. 17, 1918. Better than yesterday. At 1 p. m. today the temperature was 99.6; physical examination about as before; leukocytes 7,300; polymorphonuclears 69 per cent.; lymphocytes 24 per cent.; large mononuclears 5 per cent.; transitionals 1 per cent.; eosinophils 1 per cent.

Sept. 18, 1918. Ever since the day after starting the feeding the patient's bowels have moved from five to ten times daily; the stools being light brown and liquid. The glands are still somewhat enlarged; rash is almost gone; spleen not palpable; leukocytes 7,300.

Case 4.—J. J. W., assistant professor of plant chemistry; aged 28; married; two children.

Family History.—Mother died of phthisis; father and one sister living and well.

Personal History.—Measles, whooping cough, chickenpox and vernal ophthalmia (pink eye) as a child; no scarlet fever, diphtheria, rheumatism, tonsillitis or arthritis; with exceptions noted, always healthy; no hay fever, but has a peculiar skin rash. No boils; does not void at night; bowels regular; Wassermann negative. Red blood cells 4,136,000; hemoglobin 84 per cent.; leukocytes 4,850; polymorphonuclears 68 per cent.; lymphocytes 27 per cent.; large mononuclears 4 per cent.; transitionals 1 per cent.

Urine straw colored, neutral; specific gravity 1.025; a trace of albumin is present; no sugar.

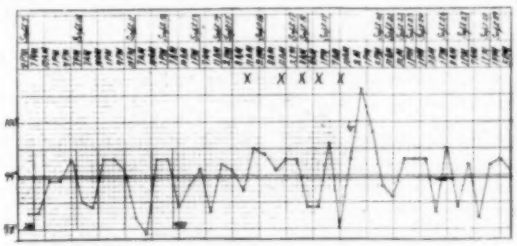

Chart 4.—Rectal temperature curve of J. J. W. Markings same as in Charts 1 and 2. Grip developed September 30 and temperatures were no longer taken.

The patient is a rather sallow individual; pupils are equal and react to light and accommodation; slight pterygium in left eye; no eye signs of exophthalmic goiter (Basedow's disease). The thyroid is palpable but no masses or nodules can be felt. The tongue is clean; throat not reddened. Except for a palpable left epitrochlear gland, which is hard and spotty, and a few palpable left inguinal glands, there is no general glandular enlargement.

Thorax well formed and symmetrical; lungs clear on auscultation and percussion.

Heart not enlarged; apex not prominent; dulness extends 4.5 cm. to the left; sounds clear. Blood pressure, maximal 110; minimal, 84; pulse rate 76.

Abdomen negative; low dulness reaches to the costal margin but the liver is not palpable; the spleen is not palpable; dulness by auscultatory percussion, 8 by 4 cm.

Skin clear except for an area of thickening and brownish induration under the left knee. No scaling or weeping. This patch is apparently eczematous. Shins clear.

Sept. 12, 1918. The patient's temperature has been ranging from 98.3 to 99.4 in the morning and is on this date 99.3. His pulse rate is 84; heart sounds clear; heart not enlarged; liver and spleen not enlarged; he has had no skin eruption. Leukocytes 5,400. A blood culture made by Dr. Larson, September 12, was negative.

Sept. 20, 1918. Since the last examination (September 12) the patient's temperature has been ranging between 99.3 and 99.6 every day. He has been hot around the face and head and has felt rather feverish; no headache,

noticeable weakness or mental dulness noted; no pains in the shins; bowels have been regular; no rash has been noted; he has had a cold for about three days of last week, but temperature remained elevated even after the cold subsided. Today there is no skin eruption, but the left epitrochlear gland is palpable, as are also several axillary glands, which are enlarged on both sides. The spleen is not palpable and the dulness has not increased.

CASE 5.—R. A. G., professor of agricultural biochemistry; aged 33; married; four healthy children.

Family History.—Mother died at 59 of pernicious anemia. Father died at 43 of "African Fever." One brother died of scarlet fever at 2 years; two brothers and one sister living and well.

Personal History.—Mumps, whooping cough, chickenpox, measles, and pleurisy in left side in 1907; tonsils removed in 1917; chronic catarrh; part of turbinates removed in 1917; no rheumatism; no skin diseases; digestion good. Fed about 300 lice one evening about third week in July.

Physical Examination.—Sept. 15, 1918. The patient is a tall, thin individual of rather sallow color, but without any trace of icterus. His gums and mucous membranes are of fair color. The thyroid is not enlarged. The tongue is coated.

The chest is symmetrical and clear on percussion, except for a slight impairment of resonance in the lower part of the left axilla. A few râles are heard throughout the chest. The heart is not enlarged. Dulness extends 5 cm. to the right of the midline and 10 cm. to the left. The sounds are clear.

The abdomen is negative. The liver and spleen are not felt. Splenic dulness, as revealed by auscultatory and light percussion, extends 10 by 5 cm., but does not reach the costal margin.

The inguinal and right submaxillary and right axillary lymph glands are palpable. The epitrochlear glands are not palpable. There is no skin eruption. The leukocytes now number 5,000; polymorphonuclears 71 per cent.; lymphocytes 22 per cent.; large mononuclears 6 per cent.; transitionals 1 per cent. (100 cells counted).

Three c.c. of the blood of S. A. G., who at that time had a well defined rash and a temperature of 99.8, were injected under the skin of the upper arm at 12:45 p. m.

Sept. 16, 1918. There was no skin reaction from the blood injection, but the patient's temperature rose to 99.2 (rectal) yesterday. His throat is, however, definitely reddened and there are small diffuse râles present over both fronts and axillae, perhaps concomitants of a general epidemic of "colds" which is rife at the time of the observation. Throat cultures are negative. Wassermann reaction negative; leukocytes 7,250.

Sept. 17, 1918. Erythrocytes 4,576,000; leukocytes 7,350. Differential count: polymorphonuclears 71 per cent; lymphocytes 24 per cent.; large mononuclears 5 per cent.

The cold subsided and the patient had no further symptoms and no eruption. The rise in temperature could not be definitely ascribed to the injection of blood.

ARBORIZATION BLOCK

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Arborization block or impaired intraventricular conduction is dependent on graphic records for its recognition. It is now generally accepted to indicate disease of the subendocardial myocardium[1] and evidences serious functional cardiac disturbance.[2] The involvement occurs in the subendocardial or Purkinje plexus.

The deflections constituting the initial ventricular complex of the electocardiogram are termed Q, R, S, and indicate the passage of the electrical impulse through the main divisions of the auriculoventricular bundle and their arborizations. These deflections comprise a graphic record which is upright in all leads, is abruptly pointed, and has a narrow base. The normal base width does not exceed 0.10 second.[3]

Arborization block is recognized by abnormal deviations of the Q, R, S group. These are increased width, notching of the apex, and splintering of the ascending and descending limbs.

The bizarre complex of arborization block is probably due either to impulse transmission through circuitous and aberrant paths or to delayed transmission through normal channels. Experimental and clinical evidence supports the former view. The abnormal complex, constituting the ventricular premature contraction (extrasystole), is well recognized, as is the complex of ventricular tachycardia and the idioventricular complex of complete auriculoventricular dissociation, which simulate the notched and widened Q, R, S group of arborization block. These we know result from ectopic stimuli which arise somewhere in the ventricular musculature and traverse aberrant paths to provoke ventricular systoles. The constancy in form of the deflections of the normal electrocardiogram make the abnormal complexes stand out as striking entities.

The present study was undertaken to determine, if possible, the significance of this disordered mechanism with especial reference to life expectancy.

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1. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**:331, 1918.

1. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429, 1917.

2. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular complex of the Electrocardiogram to Functional changes in the Heart, Arch. Int: Med. **18**:830, 1916.

3. Lewis, T.: Clinical Electrocardiography, London, Shaw, 1913, p. 32.

One hundred and thirty-eight patients with arborization block have been examined. The electrocardiographic requirements warranting this diagnosis were, (1) notching of the apex R, (2) splintering of the ascending or descending limb, and (3) in complexes of normal contour, a base width exceeding 0.10 second. These changes are summarized in Table 1.

The electrocardiograms illustrate the types represented (Figs. 1 to 10). The tension of the galvanometer fiber influences the width of the unaltered complex; a loose fiber is capable of giving an increased base width.[4]

The disorders responsible for the development of subendocardial myocardial disease are, (1) infections, (2) degenerative processes, and (3) local nutritional disturbances. These observations are summarized in Table 2.

TABLE 1.—Q, R, S—

Decade	0.06 Sec.				0.07 Sec.				0.08 Sec.				0.09 Sec.				0.10 Sec.				0.11 Sec.			
	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered
11-20	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
21-30	0	0	0	0	0	1	0	0	0	2	1	0	0	0	0	0	0	0	1	0	0	1	0	0
31-40	0	0	0	0	0	0	1	0	0	1	1	0	0	2	0	0	0	0	0	0	0	1	0	0
41-50	0	1	0	0	0	1	0	0	0	2	3	0	0	1	2	1	0	2	2	0	3	1	1	0
51-60	0	0	0	0	0	1	2	0	0	2	4	0	0	2	1	0	0	0	3	0	1	3	2	1
61-70	0	0	0	0	0	0	1	0	0	2	5	0	0	1	3	0	0	1	2	0	0	2	2	0
71-80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Endocarditis was the most frequent causative disorder, and occurred in forty-nine of the 138 cases (35.5 per cent.). Its predominance in the earlier decades of life was anticipated; degenerative and local nutritional disturbances dominate the later decades. In order of frequency are cardiovascular-renal disease with hypertension, thyrotoxic adenomas and arteriosclerosis. Exophthalmic goiter occurred in five cases. Only four proved cases of lues were found. In twenty-seven instances no tangible histories or findings suggesting causative factors were obtained.

Exertion dyspnea was a complaint in all cases, and in thirty-one (22.5 per cent.) orthopnea was a dominant symptom. Palpitation on exertion was present in forty-seven instances (34 per cent.). Twenty-two patients (15.9 per cent.) had angina pectoris and in five of these this occurred in aortic disease. Edema of the lower extremities varying

4. Hirschfelder, A. D.: Personal communication to the author.

from slight pitting in most instances to definite swelling with glazed skin in a smaller number, was present in forty-two patients (30.4 per cent.). Only five cases of general anasarca are recorded in this series. Of the edema cases twenty-four (57.1 per cent.) occurred in patients with endocardial valvular disease. The relative infrequency of edema in grave heart disease is very interesting, and emphasizes the importance of adjunct methods in the thorough examination of patients suffering from cardiac disease.

Objectively, the striking feature present in practically all of the cases is the lack of definition of the heart sounds. They are muffled, the normal differentiation between the first and second sounds is absent, and the auscultatory findings of embryocardia are simulated. There was an increase in cardiac dulness in most of our cases, both to the right and to the left of the midsternal line. Auricular fibrilla-

—Complex Changes

0.12 Sec.				0.13 Sec.				0.14 Sec.				0.15 Sec.				0.16 Sec.				0.17 Sec.				0.18 Sec.				Cases
Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	Unaltered	Notched	Splintered	Notched and Splintered	
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
0	2	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
2	3	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	31
1	5	2	1	0	0	1	2	0	3	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	41
0	4	4	0	0	0	0	0	0	2	1	3	0	1	0	0	0	2	1	1	0	0	0	0	0	0	0	1	39
0	1	2	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7
																										Total		138

tion was present in eighteen cases (13 per cent.), and occurred except in one instance in the later decades of life. Four patients had delayed auriculoventricular conduction, that is P-R intervals exceeding 0.22 second. The deflection amplitudes of the Q, R, S group showed that sixty-four patients (46.4 per cent.) had normal values (10 to 15 millivolts), sixty-one patients (44.2 per cent.) had high values, the greatest 39 millivolts, and thirteen patients (9.4 per cent.) had low values, the lowest of which was 5 millivolts. Deflections of high amplitude, largely diphasic, are believed by Carter to be indicative of a definite, totally obstructive, temporary or permanent lesion of one of the branches of the auriculoventricular bundle; those of low amplitude suggest diffuse sclerosis, although they do not preclude localized lesions of the main branch and its arborizations.

No striking changes in amplitude of the final T-wave of the ventricular complex were noted. This wave was negative in eighty-five

cases (63 per cent.), and occurred most frequently in Lead 1 alone, in forty-two cases (49.4 per cent.). Table 3 shows the T-wave negatively in this series. The inversion of the T-wave in Lead 1 is significant, I believe, and of itself indicative of myocardial changes, for in all the electrocardiograms studied in which this observation was noted,

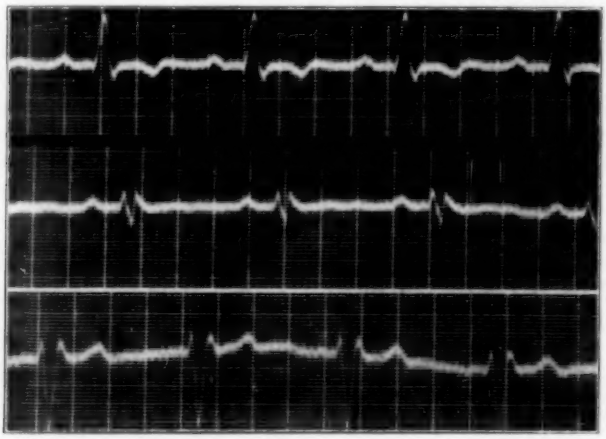

Fig. 1.—Rate 65. Q, R, S complex widened in Leads 1 and 3 0.11 sec. and splintered in Lead 2. Inverted T-wave, Lead 1. Left ventricular preponderance. Case 160997.

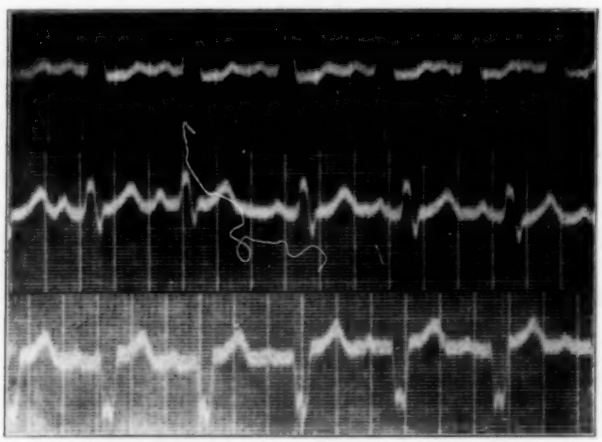

Fig. 2.—Rate 100. Q, R, S complex notched and widened 0.12 sec. Left ventricular preponderance. Case 213193.

the patients presented definite clinical evidence of myocardial insufficiency, except in one case, in which the conclusions were indefinite.

One hundred and twelve patients with arborization block have been heard from in answer to letters of inquiry. Seventy-eight (69.6 per cent.) of these have died; all except three died of heart disease. The average duration of life from the time of examination was eight

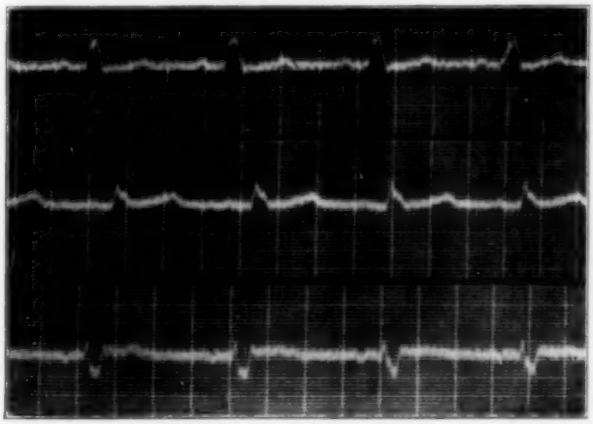

Fig. 3.—Rate 66. Q, R, S complex notched. Left ventricular preponderance. Case 154767.

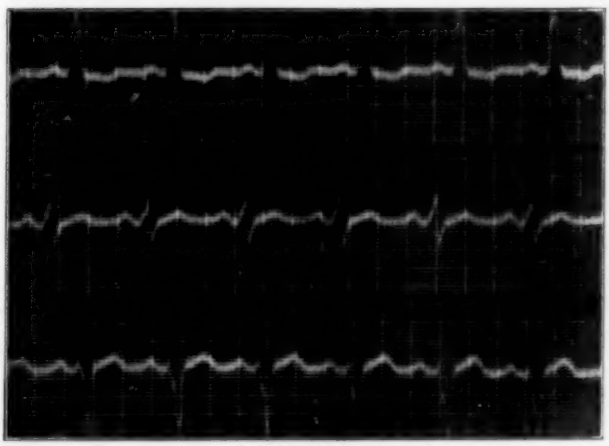

Fig. 4.—Rate 82. Q, R, S complex splintered and widened 0.11 sec. Left ventricular preponderance. Case 165664.

and one-half months. These statistics bear out the presumption that arborization block is a grave disorder. It is well recognized that disease involving the conduction system is a serious menace to life, but arborization block is attended by an earlier mortality than that caused by the lesions higher up. As life is directly dependent on ventricular action, any impairment of ventricular function is grave. The deaths are summarized in Table 4.

Thirty-four patients of the series are known to be alive; of these, seventeen are worse, four of them bed-ridden; nine report their conditions unchanged and eight report some improvement. We were

TABLE 2.—ETIOLOGIC DISEASES

Decade	Endocarditis	Percentage	Cardiovascular-Renal	Percentage	Thyrotoxic Adenomas	Percentage	Exophthalmic Goiter	Percentage	Arteriosclerosis	Percentage	Syphilis	Percentage	No Etiologic History
11-20	2	100.0	0	0	0	0	0	0	0	0	0	0	0
21-30	8	80.0	1	10.0	0	0	1	10.0	0	0	0	0	0
31-40	5	62.5	0	0	0	0	0	0	0	0	1	12.5	2
41-50	14	45.2	10	32.3	0	0	1	3.2	0	0	2	6.5	6
51-60	10	24.4	14	34.1	6	14.6	2	4.8	0	0	1	2.4	9
61-70	8	20.5	17	43.6	2	5.1	1	2.6	2	5.1	0	0	9
71-80	2	28.6	2	28.6	1	14.2	0	0	1	14.2	0	0	1
	49		44		9		5		3		4*		27

* Three cases under syphilis classified under endocarditis.

TABLE 3.—T-WAVE NEGATIVITY

Decades	Lead 1	Lead 2	Lead 3	Leads 1 and 2	Leads 2 and 3	Leads 1, 2 and 3	Total
11-20	1	0	0	0	0	0	1
21-30	0	1	2	2	1	0	6
31-40	1	0	3	1	0	0	5
41-50	8	0	1	2	2	0	13
51-60	14	0	3	3	6	1	27
61-70	16	0	3	5	1	4	29
71-80	2	0	0	1	1	0	4
	42	1	12	14	11	5	85

TABLE 4.—SUMMARY OF DEATHS

Decade	Total Cases	Deaths
11-20	2	1
21-30	10	3
31-40	8	5
41-50	31	16
51-60	41	24
61-70	39	23* †
71-80	7	6*
Total	138	78

* Died of cancer. † Died of pneumonia.

afforded the opportunity of five necropsies; the cardiac findings are appended. No definite localizing lesions were found, but rather diffuse degenerative processes involving the myocardium.

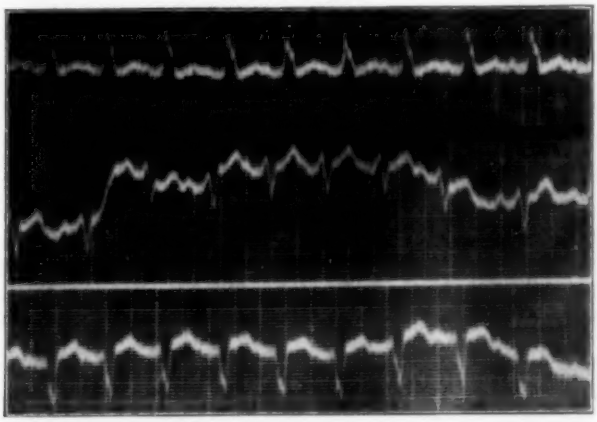

Fig. 5.—Rate 112. Q, R, S complex splintered and widened 0.12 sec. Left ventricular preponderance. Case 176302.

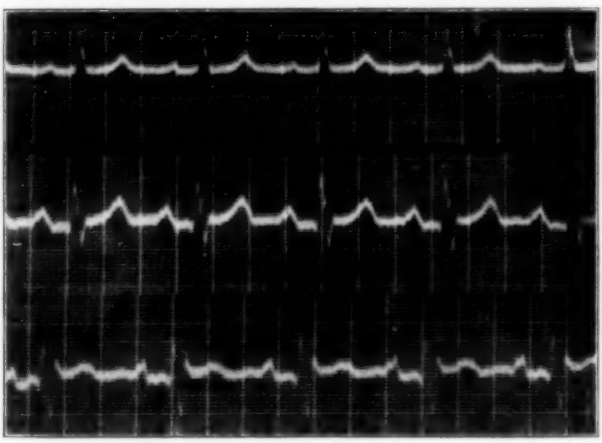

Fig. 6.—Rate 75. Q, R, S complex splintered 0.08 sec. Left ventriclular preponderance. Case 162663.

Case 1 (130119).—Very marked fatty changes in the myocardium; marked dilatation of the aortic, mitral and tricuspid valvular rings of the heart; moderate nodular fibrous and fatty thickening of the lining of the aorta, and of the aortic and mitral leaflets of the heart; marked thinning of the myo-

cardium of the left ventricle; marked dilatation and engorgement of all of the chambers of the heart; moderate hydropericardium. Histologic Findings: Fragmentation and slight fatty changes.

CASE 2 (147045).—Obliterative fibrous adhesive pericarditis; marked nodular sclerosis and fatty changes in the lining of the aorta and its main

Fig. 7.—Rate 82. Q, R, S complex notched and widened 0.14 sec. Inverted T-wave, Lead 1. Left ventricular preponderance. Case 216281.

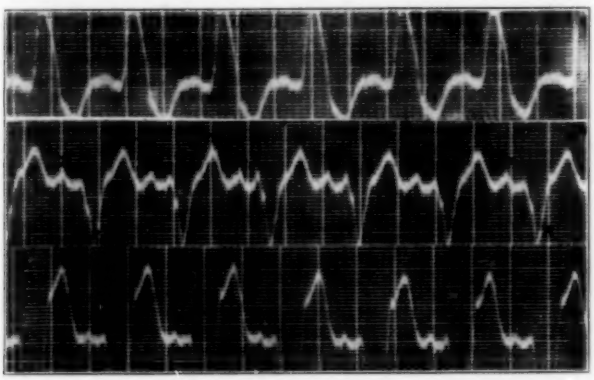

Fig. 8.—Rate 115. Q, R, S complex splintered and widened 0.16 sec. Inverted T-wave Lead 1. Left ventricular preponderance. Case 143010.

branches; marked calcareous sclerosis of the coronary arteries; huge spontaneous thrombosis of the dependent portion of the left ventricle; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers of the heart; moderate dilatation of the aortic and mitral valvular rings; marked diffuse thickening of the pulmonary artery. Histologic Findings:

The pericardium was thickened and adherent to the heart. There was a marked replacement of the heart muscle by fibrous tissue. Toward the lower portion was seen hyalinization of the muscle. The thrombus was made up of fibrin and in places showed a slight infiltration of leukocytes. With the fat stain considerable fat was found in the thrombus.

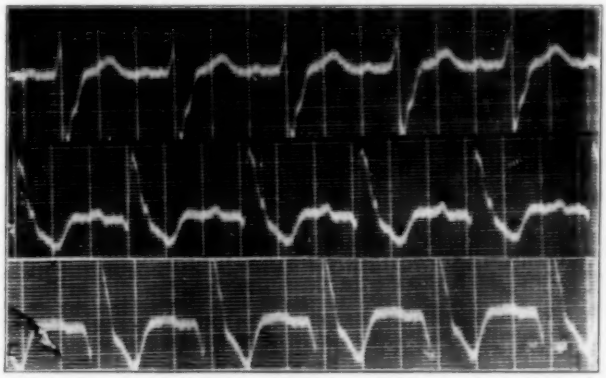

Fig. 9.—Rate 86. Q, R, S complex notched, splintered and widened 0.12 sec. Inverted T-wave, Leads 2 and 3. Right ventricular preponderance Case 142757.

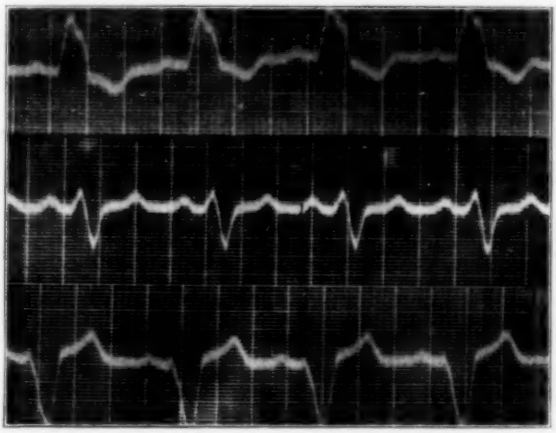

Fig. 10.—Rate 75. Q, R, S complex notched and widened 0.16 sec. Inverted T.-wave, Lead 1. Left ventricular preponderance. Case 154081.

Case 3 (161776).—Marked fatty degeneration of the myocardium; marked hydropericardium; moderate dilatation of the heart. Histologic Findings: In the heart there were marked fatty degeneration and fragmentation; moderate increase in fibrous connective tissue and hypertrophy of the muscle.

Case 4 (189701).—Acute dilatation of the heart; marked fatty and fibrous sclerosis of the lining of the aorta and of the aortic and mitral valvular leaf-

lets; petechial hemorrhages in the visceral pericardium. Histologic Findings: Moderate diffuse fatty degeneration of the myocardium. Aortitis probably luetic; fibrous and fatty changes in the intima and media, with round cell infiltration.

CASE 5 (197468).—Marked fatty and fibrous diffuse parenchymatous myocarditis; marked hypertrophy of the myocardium of the left ventricle; marked dilatation of all the chambers and valvular rings of the heart; spontaneous mural thrombosis of the left ventricle; slight hydropericardium. Histologic Findings: Fatty and fibrous degeneration of the myocardium.

SUMMARY

1. Arborization block is a grave disorder of the cardiac mechanism; it entails a large and early mortality (69.6 per cent.), in an average duration of eight and one-half months.

2. Disorders responsible for the development of this condition were found to be, in order of frequency, (1) infections, (2) degenerative processes, and (3) local nutritional disturbances.

3. The relative infrequency of edema was a striking observation.

4. The lack of definition and differentiation between the first and second heart sounds was constantly observed.

THE BASAL METABOLISM IN ANEMIA WITH ESPECIAL REFERENCE TO THE EFFECT OF BLOOD TRANSFUSION ON THE METABOLISM IN PERNICIOUS ANEMIA *

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HISTORICAL

In spite of critical reviews of the investigations on metabolism in anemia published by Strauss,[1] in 1906, and Meyer and DuBois,[2] in 1916, it will be profitable to discuss again the material which has been presented.

1. *Animal Experimentation.* — Work on metabolism in anemic animals has concerned itself almost entirely with posthemorrhagic conditions. Thus Bauer,[3] under the complex disturbances immediately following blood loss, found the metabolism slightly diminished; Delchef[4] found it normal or slightly diminished; Finkler[5] and Pembrey and Gürber[6] found it normal; Fredericq[7] found it transiently diminished and then elevated; Lukjanow[8] and Hári[9] found it elevated. Bauer[3] reported a remarkably diminished metabolism a few days after bleeding. His work has been justly criticized by Pembrey and

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1. Straus, H.: Cf. von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, **1**:881, 1906.

2. Meyer, A. L., and DuBois, E. F.: The Basal Metabolism in Pernicious Anemia, Arch. Int. Med. Part 2, **17**:965, 1916.

3. Bauer, J.: Ueber die Zersetzungsvorgänge im Thierkörper unter dem Einflusse von Blutentziehungen, Ztschr. f. Biol. **8**:567, 1872.

4. Delchef, J.: Influence de la saignée et de la transfusion sur la valeur des échanges respiratoires, Arch. internat. de physiol. **3**:408, 1905-1906.

5. Finkler, D.: Ueber den Einfluss der Strömungsgeschwindigkeit und Menge des Blutes auf die thierische Verbrennung, Arch. f. d. ges. Physiol. **10**:368, 1875.

6. Pembrey, M. S., and Gürber, A.: On the Influence of Bleeding and Transfusion on the Respiratory Exchange, Jour. Physiol. **15**:449, 1894.

7. Fredericq, L.: De l'action physiologique des soustractions sanguines, Travaux du Laboratoire, **1**:133, 1885-1886.

8. Lukjanow, S.: Ueber die Aufnahme von Sauerstoff bei erhöhtem Procentgehalt desselben in der Luft, Ztschr. f. physiol. Chem. **8**:313, 1884.

9. Hári, P.: Der Einfluss grosser Blutverluste auf die Kohlensäure- und Wasserausscheidung und Wärmeproduktion, Arch. f. d. ges. Physiol. **130**:177, 1909.

Gürber,[6] who found no changes from the time of hemorrhage until recovery, and their findings are apparently verified by Hári,[9] who has reported so slight an elevation during the period of recovery as to fall within normal limits. In the experiments of Pembrey and Gürber[6] the removed blood was at once replaced by saline solution, a procedure which they term "transfusion." Delchef[4] and Hári[10] have reported the only studies on true transfusion. Immediately after the anemic animal received the injected blood Delchef[4] found the oxygen consumption greatly elevated, and attributed this to the agitation and dyspnea attendant on the operation rather than to direct effects from increased blood content. Hári[10] found the metabolism somewhat increased on injection of fresh blood into normal animals. His results may also be attributed to the agitation resulting from the operation or to the actual food received by the animal in the form of the injected plasma.

The diversity of results which all these observations record, while undoubtedly due in part to determinations of the metabolism too soon after the excitement attendant on hemorrhage, is largely due to failure on the part of the observers to take uniform and adequate precautions in regard to food, muscular activity and apparatus.

2. *Clinical Observations.* — The same technical considerations coupled with lack of normal standards have caused a large part of the disagreement found in metabolic studies on clinical anemias. On the basis of Meeh's formula for surface area and the normal of 34.7 calories per square meter per hour, Meyer and DuBois[2] have recalculated the basal metabolism on certain clinical anemias studied prior to their own work. They found that not only the pioneer work of Pettenkofer and Voit,[11] but that of all authors on leukemia shows a considerably elevated metabolism. They also found that the data of Kraus and Chvostek[12] and Bohland[13] on anemias in general give values above or on the upper limits of normal. It should be noted that both of these observers provided experimental conditions which are now known to increase the metabolism. Thiele and Nehring[14] have reported a normal metabolism for secondary anemia, but diminished or on the lower border of normal for chlorosis. For their one case

10. Hári, P.: Ueber den Einfluss der intravenösen Bluttransfusion auf den Stoff- und Energieumsatz, Biochem. Ztschr. **34**:111, 1911; **44**:1, 1912.

11. Pettenkofer, M. v., and Voit, C.: Ueber den Stoffverbrauch bei einem leukämischen Manne, Ztschr. f. Biol. **5**:319, 1869.

12. Kraus, Fr., and Chvostek, Fr.: Ueber den Einfluss von Krankheiten, besonders von anämischen Zuständen, auf den respiratorischen Gaswechsel, Ztschr. f. klin. Med. **22**:449, 1893.

13. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl. klin. Wchnschr. **30**:417, 1893.

14. Thiele, O., and Nehring, O.: Untersuchungen des respiratorischen Gaswechsels unter dem Einflusse von Thyreoideapräparaten und bei anämischen Zuständen des Menschen, Ztschr. f. klin. Med. **30**:41, 1896.

of pernicious anemia our computations, also based on Meeh's formula and 34.7 calories, show a gradual and unexplained drop in metabolism from the upper to the lower border of normal over a duration of two weeks. The anemias studied by Magnus-Levy[15] show a normal calorific output with the exception of a slight elevation in one case of pernicious anemia and an equally slight diminution in one case of secondary anemia. He also found a small drop in metabolism in two chlorotic, one secondary and one leukemic case under treatment with iron preparations, and under the same conditions a slight rise in one of secondary anemia. Basing their computations on modern standards, Meyer and DuBois[2] found their own cases of pernicious anemia gave a metabolism on the upper limits of normal in mild types, and definitely elevated in severe ones. Their worst case, on observations repeated over an interval of time, showed a drop in metabolism accompanied by a fall in temperature and pulse rate. Grafe[16] and Eberstadt[17] attempted to correlate the blood forming ability of anemic animals with the metabolism. They found that rabbits with exhausted marrow from hemorrhagic anemia or from anemia due to phenylhydrazin injections had diminished metabolism, while those anemic but with normal marrow showed normal metabolism. Rolly[18] contradicts these findings on animals and adds observations on clinical anemias. Our computations of his figures, again based on Meeh's formula and 34.7 calories, show a metabolism considerably elevated for pernicious anemia and for an aplastic type of anemia due to carcinoma, on the upper level of normal for chlorotic and hemorrhagic anemia, on the lower level for secondary anemia due to lead poisoning, and diminished for one due to parasitic infection. Grafe,[19] stimulated by his animal work to belief in the influence of active blood formation in increasing metabolism, carried his observations into the clinic. Contrary to Rolly[18] he suggested that the same relation seemed to hold, since two of the most severe cases of pernicious anemia with signs of marrow insufficiency gave the lowest values in his series, and a third case gave a much higher metabolism during a blood crisis than subsequently when regeneration was less active. According to our computations, the two first cases had a metabolism on the lower border of normal,

15. Magnus-Levy, A.: Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhezustand, Ztschr. f. klin. Med. **60**:177, 1906.

16. Grafe, E.: Beiträge zur Kenntnis der Kompensations- einrichtungen bei chronischen experimentellen Anämien, München. med. Wchnschr. **51**:2840, 1912.

17. Eberstadt, F.: Ueber den Einfluss chronischer experimenteller Anämieen auf den respiratorischen Gaswechsel, Arch. f. exper. Path. u. Pharmakol. **71**:329, 1912-1913.

18. Rolly, Fr.: Ueber den respiratorischen Gaswechsel bei chronisch anämischen Zuständen, Deutsch. Arch. f. klin. Med. **114**:605, 1914.

19. Grafe, E.: Zur Kenntnis des Gesamtstoffwechsels bei schweren chronischen Anämien des Menschen, Deutsch. Arch. f. klin. Med. **118**:148, 1915.

while the third case had an elevated metabolism during the crisis and was normal during the period of moderate regeneration.

It is evident from this review that with the exception of leukemia, no definite conclusions have been obtained concerning the metabolism in anemia. Not only has there been no agreement from case to case, but in one and the same patient with similar experimental conditions, the results have shown wide variations; and unfortunately the time relations of metabolism determination to clinical treatment and blood picture in any such case have not been sufficiently noted to make explicable the changes seen from date to date in the calorific output. On the whole, however, experimental data have given evidence of a tendency toward increased metabolism in anemias of all types.

Many explanations for this increase have been given. They fall into two groups in relation to the experimental solution of the problem:

1. The increased muscular work required by the more rapid respiration and heart rate have been considered in most cases sufficient to cause such increases in metabolism as have been observed, with the exception of leukemia. This explanation depends on simple muscular compensation and demands no consideration of obscure toxic factors. metabolism of young red cells, etc.

2. The increased metabolism of young and nucleated red cells, unusual numbers of white cells, undetermined toxic influences and activity of the blood forming centers have, with other possibilities, been cited as causes of the increased metabolism. None of these causes is definitely compensatory.

If the grade of the metabolism in anemia is due in any degree to the increased muscular work which the disease requires, it should be possible by reducing the heart rate and respiration to normal to gain a true picture of the uncompensated normal metabolism of the case. Blood transfusion, by an almost instantaneous check to the accelerated heart and lung action in these patients, restrains the muscular compensation. We have been able to find no record of work on the gaseous exchange under these conditions, and as transfusion was being employed by two of us[20] in the treatment of anemia, an exceptional opportunity for metabolic study was offered.

EXPERIMENTAL METHODS

1. *Transfusions.*—The technic employed is discussed in a previous article.[20] It is of interest to note that the patients have received transfusions of whole blood and transfusions of washed red cells suspended in physiologic salt solution. The effect of both types of transfusion is the same—a decrease in metabolism. It should be noted that in the transfusions of washed red cells

20. Drinker, C. K., and Brittingham, H. H.: Cause of the Reactions Following Transfusion of Citrated Blood, Arch. Int. Med. To be published.

we have provided the simplest possible conditions—an increase in circulating hemoglobin without introduction of material which can be burned, as is inevitable in introduction of plasma.

2. *Metabolism Determinations.*—For the metabolic study a combination of the Douglas and Tissot[21] methods was employed. The half mask and modified valves as supplied by Siebe Gorman & Co. were used in connection with a modified Tissot spirometer. The latter is made of aluminum, has a syphon counterpoise, but a constant volume water bath so that corrections must be made for the displacement.

Two portable Haldane gas analyzers[22] were used for the analyses of the expired air. Duplicate analyses were made on every period of a determination. After each day's analyses, air was drawn through the outdoor tube and analyzed. This checked at once the patient's inspired air and the accuracy of the analyses on his expired air.

Without leaving his bed, the patient was wheeled to the laboratory from fourteen to sixteen hours after his last nourishment—a light supper—and eight or more hours after his last drink of water. There the metabolism nurse took charge of his comfort. He lay on his back with never more than two soft pillows under his head, and with perhaps one under back or knees. Pulse and respirations were taken every three minutes until such time as the chart showed constancy—an interval never less than twenty minutes, usually thirty. The mask was then tied in position and five minutes elapsed before the first period was begun. This was found to be time enough to overcome any effects due to the excitement of the adjustment of the mask. The period was run nine to ten minutes. A kymographic record of the respiration was made throughout and all movements possible of detection were recorded. At the end of the period the mask was removed, the buccal temperature was taken and the patient was permitted to make slight movements. In about ten minutes the mask was again placed in position; this time the patient exhaled into the room for but one minute and a second period was carried through exactly as the first. We prefer this double placement of the mask as it enables us to detect readily any possible leak. When muscular and nervous activity are ruled out and the two periods agree satisfactorily we are sure that the mask was air tight. At the end of the second period the patient's height and weight were taken and he was returned to the ward.

The respiration rate and volume per respiration were established from the pneumographic records. The percentage normality of the metabolism was based on the DuBois linear formula[23] and the corresponding standards of normal calorific output.[24] Use of these standards was governed not by our conviction of their finality, but by our belief that at present they form the best basis for presentation of the material we have to offer. The nitrogen metabolism was not studied. The nonprotein respiratory quotient,[25] however, was used to compute the total heat production. Benedict[26] has shown that

21. Carpenter, T. M.: A Comparison of Methods for Determining the Respiratory Exchange of Man, Carnegie Institution of Washington, Publication 216, 1915, p. 61.

22. Haldane, J. S.: Methods of Air Analysis, London, 1912.

23. DuBois, D., and DuBois, E. F.: A Formula to Estimate the Approximate Surface Area if Height and Weight be known, Arch. Int. Med., Part 2, **17**:863, 1916.

24. Aub. J. C., and Dubois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. Part 2, **19**:823, 1917 (page 831 only).

25. Lusk, G.: The Science of Nutrition, Ed. 3, Philadelphia, W. B. Saunders Co. 1917, p. 61.

26. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Carnegie Institution of Washington, Publication 261, 1918, p. 203.

such a method of computation ordinarily causes an error in percentage normality of from 1 to 2 per cent. While this could in no way affect agreement between closely following periods, it might easily do so between the results of different days. We, therefore, consider that in order to be significant, a change in the metabolism on different days must show a variation of the averages of at least 5 per cent., while in any one determination the two periods, to be satisfactory, must vary by not more than 3 per cent.

TABLE 1.—METABOLISM STUDIES ON—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Metabolism		
					Date	Height, Cm.	Weight, Kg.
1 M. C.	7552	Pernicious anemia; chronic type; duration July, 1915 to November, 1917; no remissions	♂	53	11/15/17	164.1	59.0
2 L. A. T.	7793	Pernicious anemia; chronic type; duration August, 1916 to January, 1918; remission September, 1917, to November, 1917	♂	46	1/ 4/18	173.2	70.7
3 M. A. O.	8448	Pernicious anemia; chronic type; duration April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	4/15/18	158.6	49.1
4 A. J. N.	5811	Necropsy diagnoses: Emaciation; hyperplasia of lymphatics of small intestine and mesenteric glands; atrophy of liver and spleen; congestion of kidney; Meckel's diverticulum. Chronic anemia; duration June, 1915 to January 1917; progressing slowly and without remission	♂	42	1/16/17	175.0	58.4
5 J. F. G.	8473	Secondary anemia; carcinoma of stomach; hypertension; duration of anemia, April, 1917 to April, 1918; progressing slowly and without remission	♂	59	4/12/18	169.1	57.0
6 E. K.	8191	? Pernicious anemia; neuritis; dilation aortic arch; syphilis; fever (cause unknown); duration of anemia, November, 1917 to March, 1918; progressing slowly and without remission	♀	58	3/23/18	158.4	53.3
7 L. K.	6951	Pernicious anemia; chronic type; furunculosis; duration July, 1916 to August, 1917; no remissions	♂	73	8/13/17	165.8	50.4
8 A. H. P.	8220	Pernicious anemia; acute type; duration, February, 1918 to March, 1918	♂	58	3/ 6/18	177.4	67.3
9 F. D.	8024	Pernicious anemia; chronic type; duration January, 1917 to May, 1918; one remission March, 1917 to January, 1918	♀	42	5/10/18	162.0	64.3
10 A. S.	7470	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	11/10/17	160.2	48.3
11 J. J. M.	8140	Banti's disease; bronchitis; duration of anemia, December, 1917 to February, 1918; no remissions	♂	33	2/28/18	178.0	77.6
12 G. A. C.	7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	12/26/17	155.9	41.8
13 W. E. M.	8192	Pernicious anemia; chronic type; laryngitis; duration January, 1915 to February, 1918; diagnosed pernicious anemia January, 1915; had long and rather complete remission during years of 1916-1917	♂	58	3/ 2/18	175.5	59.7
14 T. G. H.	8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	3/ 7/18	164.7	39.5
15 E. F. M.	8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	3/ 8/18	170.6	59.7
16 A. J. C.	7406	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	10/23/17	157.0	56.6
17 E. M.	7586	Secondary anemia; carcinoma of stomach; abdominal metastases; duration of anemia, June, 1917 to November, 1917	♂	41	11/23/17	175.3	55.5
18 E. M. C.	8040	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death May, 1918	♀	29	2/10/18	150.1	40.7

† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 6 per cent.

PRESENTATION OF DATA

In the accompanying tables we have given the average data of the two periods of a day's determination and have pointed out cases in which the parallel periods did not fall within the 3 per cent. limit. In most cases a determination of metabolism was made before any type

of treatment was undertaken. Exceptions are noted in Table 3. The metabolism was then followed from time to time during spontaneous improvement or in connection with the transfusions. Of necessity a number of patients received an original determination before treatment, but could be studied no further. Such cases we have placed in

—Untreated Cases of Anemia

Metabolism								Blood Picture						
Buccal Temperature, F.	Pulse	Respiration	Volume per Minute, L.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Lhear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	Remarks
98.6	70	9.8	4.02	186	0.75	52.7	—15	11/16/17	98	4.3	6,700	0	++	+	Many macrocytes seen
98.6	67	9.3	4.31	215	0.78	61.5	—13	1/ 3/18	69	2.3	6,000	0	++	++	
98.8	80	14.9	4.56	159	0.75	45.1	—11	4/15/18	30	1.0	5.000	0	++	0	
98.2	69	11.0	4.93	219	0.80	63.1	— 4	1/17/18	73	2.9	6.600	2	+	+	
97.0	69	14.3	6.33	210	0.76	59.8	— 4	4/11/18	50	3.0	18,800	0	+	+	
98.6	72	20.2	4.55	187	0.74	53.1	— 2	3/20/18	60	3.1	4,600	0	+	0	Plate counts: March 23, 148,000 March 26. 184,000
98.8	66	16.7	5.70	193	0.73	54.6	— 1	8/12/17	35	1.5	3,800	16	++	++	10 megaloblasts in the 16 blasts seen in counting 100 leukocytes
99.2	95	16.3	6.00	247	0.77	70.4	+ 2	3/ 7/18	39	0.9	5,000	0	++	0	
99.0	84	16.0	5.84	221	0.77	63.2	+ 5	5/ 9/18	40	2.5	6,100	0	+	+	
98.6	61	19.1	5.22	209	0.73	59.1	+ 5	11/ 8/17	68	3.0	4,800	0	0	0	Splenectomy showed large splenitis
98.6	90	13.5	7.11	293	0.75	83.3	+ 8	2/25/18	75	2.8	3,000	0	0	0	Plate count 66,000; patient died May, 1918; no necropsy
99.4	72	13.7	4.50	182	0.76	51.8	+ 9†	12/23/17	40	1.5	6,700	0	0	0	Plates decreased; patient rarely showed blasts
98.4	71	17.5	6.51	253	0.76	72.1	+11	3/ 2/18	41	1.4	7,000	0	+	+	
99.2	102	18.4	5.11	198	0.74	56.2	+11	3/ 6/18	30	2.2	3,800	0	+	+	Patient recovered with 1 transfusion and iron medication
100.0	101	22.1	6.55	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megaloblast seen
98.8	97	14.6	5.42	217	0.75	61.5	+15‡	10/22/17	68	3.6	7,000	0	+	+	Patient developed large splenic tumor; death April. 1918; no necropsy
98.8	87	11.9	5.31	265	0.71	74.5	+16	11/20/17	36	3.7	11,400	2	++	++	
102.8	118	17.8	5.50	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	++	

Table 1, together with the original determination of all cases studied during treatment. Table 1 thus tabulates the data of the metabolism studies on our untreated anemias, together with that necessary for an estimation of the clinical picture and for the basis of computations.

Table 2 is so arranged as to show in detail the data and time relations of metabolism to treatment and blood picture in a complete course of study on six characteristic patients.

Table 3 gives the admission and the end data on the remainder of our cases studied during a course of treatment.

TABLE 2.—Relation of Metabolism to—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Treatment: Description	Dates Metabolism and Treatment	Metabolism: Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
1 M. C.	7552	Pernicious anemia; chronic type; duration, July, 1915 to November, 1917; no remissions	♂	53	.....	11/15/17	164.1	59.9	98.6	70	9.8
					700 c.c. washed R.B.C. in physiol. saline	11/16/17					
					600 c.c. washed R.B.C. in physiol. saline	11/18/17					
						11/19/17	.....	60.3	98.4	66	12.1
					550 c.c. washed R.B.C. in physiol. saline	11/21/17					
						11/26/17	.....	59.7	97.8	60	10.6
						12/ 5/17	.....	59.7	98.4	65	9.3
3 M. A. O.	8448	Pernicious anemia; chronic type; duration, April, 1917 to April, 1918; yellow pallor of skin noticed first April, 1918; no remissions	♀	62	.....	4/15/18	158.6	49.1	98.8	80	14.9
					900 c.c. washed R.B.C. in physiol. saline	4/16/18					
						4/17/18	.....	48.5	98.0	73	18.5
					900 c.c. washed R.B.C. in physiol. saline	4/18/18					
						4/20/18	.....	48.6	98.0	68	15.9
					800 c.c. washed R.B.C. in physiol. saline	4/29/18	.....	50.8	98.2	72	13.8
						4/30/18	.....	49.3	99.2	70	13.0
12 G. A. C.	7739	Pernicious anemia; chronic type; arteriosclerosis; ventral hernia; duration, February, 1916 to March, 1918; remission September, 1917 to November, 1917	♀	59	.....	12/26/17	155.9	41.8	99.4	72	13.7
					600 c.c. washed R.B.C. in physiol. saline	1/ 6/18					
						1/ 9/18	.....	40.8	99.0	85	13.2
						1/16/18	.....	39.3	99.2	80	14.0
						2/ 7/18	.....	41.8	99.0	79	13.3
					150 c.c. plasma and platelets.....	2/24/18					
					700 c.c. washed R.B.C. in physiol. saline	2/25/18	.....	39.9	99.6	87	13.8
						2/26/18	.....	40.2	98.4	72	12.4
					700 c.c. washed R.B.C. in physiol. saline	2/28/18	.....	40.1	98.6	74	12.9
					135 c.c. plasma and platelets.....	3/ 1/18					
						3/ 5/18	.....	40.6	98.6	66	13.6
14 T. G. H.	8204	Secondary anemia (brief duration); menorrhagia; duration of anemia, September, 1917 to March, 1918	♀	35	.....	3/ 7/18	164.7	39.5	99.2	102	18.4
					750 c.c. washed R.B.C. in physiol. saline	3/21/18	.....	39.0	99.4	84	16.3
						3/25/18	.....	39.1	98.4	67	16.1
15 E. F. M.	8217	Pernicious anemia; acute type; duration of anemia, February, 1918 to March, 1918; no remissions	♀	56	.....	3/ 8/18	170.6	59.7	100.0	101	22.1
					950 c.c. washed R.B.C. in physiol. saline	3/10/18					
					900 c.c. washed R.B.C. in physiol. saline	3/12/18					
					500 c.c. washed R.B.C. in physiol. saline	3/14/18					
						3/15/18	.....	61.8	98.6	77	24.0
					900 c.c. washed R.B.C. in physiol. saline	3/19/18					
						3/20/18	.....	61.7	98.6	77	22.7
						3/25/18	.....	60.9	98.6	83	21.7
					450 c.c. washed R.B.C. in physiol. saline	4/ 2/18	.....	59.4	98.8	80	20.6
					450 c.c. washed R.B.C. in physiol. saline	4/ 4/18					
						4/ 5/18	.....	59.5	97.6	74	20.1
						4/ 9/18	.....	59.9	98.6	78	20.1
18 E. M. C.	8040 8337	Pernicious anemia; chronic type; febrile and dangerously ill at present; anemia first noted June, 1916; complete remission January, 1917 to August, 1917; gradual decline August, 1917 to February, 1918; death, May, 1918	♀	29	800 c.c. washed R.B.C. in physiol. saline	2/10/18	150.1	40.7	102.8	118	17.8
					825 c.c. washed R.B.C. in physiol. saline	2/13/18					
					675 c.c. citrated whole blood.....	2/15/18					
						2/16/18	.....	40.0	97.8	55	12.6
						3/26/18	.....	39.4	100.6	102	14.2
					800 c.c. washed R.B.C. in physiol. saline	3/29/18					
						3/30/18	.....	39.6	98.8	79	14.0

* The two periods disagreed by 6 per cent.
† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 5 per cent.
§ The two periods disagreed by 4 per cent.

DISCUSSION OF RESULTS

A survey of Table 1 — the data on the untreated cases — reveals the same irregularities found throughout the literature. The metabolism falls in part within normal limits, in part above and below

normal. It is parallel neither with the marrow activity as represented by the blood picture, history and general condition of the patient, nor

—Treatment in Six Cases of Anemia

Metabolism						Blood Picture						
Respiration	Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R. C.	Anisocytosis	Poikilocytosis	Remarks
9.8	4.02	410	186	0.75	52.7	—15	11/13/17	87	3.2	8,400	0	++	+	Plates decreased. Many macrocytes
							11/18/17	96	4.0	8,500	0	++	+	Many macrocytes
							11/26/17	104	4.5	5,400	0	+	0	
12.1	3.93	327	179	0.81	51.6	—17	12/ 5/17	83	5.4	6,200	8	+	0	Eight normoblasts
10.6	3.62	344	161	0.80	46.2	—26								
9.3	3.60	388	161	0.78	45.9	—26								
14.9	4.56	307	159	0.75	45.1	—11	4/15/18	30	1.0	5,000	0	++	+	
							4/17/18	55	1.9	2,400	0	0	0	One myelocyte seen on this date
18.5	5.12	277	163	0.72	45.8	— 8	4/20/18	90	3.4	3,800	2	0	0	One normoblast, one megaloblast seen
							4/29/18	75	3.2	3,200	0	0	0	Rare stippled cells present
15.9	4.48	283	152	0.75	43.3	—14	4/30/18	75	3.3	3,300	1	0	0	Four myelocytes seen
13.8	4.58	319 *	153	0.85	44.6	—13								
13.0	4.13	318	148	0.84	43.1	—14*								
13.7	4.50	329	182	0.76	51.8	+ 9†	12/29/17	40	1.2	6,600	1	+	++	One myelocyte, one normoblast
							1/ 7/18	44	2.1	4,000	0	+	+	Marked stippling
13.2	3.93	298	170	0.76	48.4	+ 3‡	1/14/18	45	2.2	5,300	0	+	+	
14.0	3.60	258	155	0.72	43.6	— 7	2/ 6/18	60	2.4	8,200	0	+	0	
13.3	3.99	301	166	0.76	47.1	— 2	2/26/18	58	2.2	3,400	0	0	+	Polychromatophilia constant in this patient
13.8	4.16	302	168	0.75	47.8	+ 2								
12.4	4.25	344	169	0.77	48.3	+ 3§								
12.9	4.20	325	156	0.78	44.5	— 5								
13.6	3.95	290	149	0.81	42.9	— 9								
18.4	5.11	278	198	0.74	56.2	+11	3/ 6/18	30	2.2	3,800	0	+	+	Plate count, March 3, 254,000
16.3	4.88	300	183	0.79	52.4	+ 4	3/20/18	46	4.2	7,800	0	0	+	Many macrocytes
16.1	4.19	260	160	0.78	45.7	—10	3/25/18	74	4.9	5,600	0	+	+	Few polychromatophilic, stippled cells present
22.1	6.55	297	241	0.73	68.0	+15	3/ 7/18	25	0.8	2,500	1	++	++	One megaloblast. Polychromatophilia slight
							3/15/18	64	2.4	1,800	0	+	+	
							3/22/18	70	2.8	3,100	1	+	+	Macrocytes numerous
							3/25/18	70	3.2	2,400	0	+	+	Macrocytes numerous
24.6	6.52	266	216	0.79	62.0	+ 3	4/ 1/18	64	3.1	2,900	0	+	+	Macrocytes numerous
							4/ 5/18	75	3.5	4,800	0	+	+	No polychromatophilia nor stippling
23.7	6.12	258	213	0.77	60.7	+ 1	4/ 9/18	95	4.0	4,200	0	+	+	No polychromatophilia nor stippling
21.7	5.72	264	212	0.80	61.0	+ 2								
20.6	5.89	286	225	0.79	64.6	+10								
20.1	5.77	287	217	0.81	62.8	+ 6								
20.1	5.51	275	213	0.80	61.3	+ 3¶								
17.8	5.50	309	205	0.75	58.1	+20	2/ 8/18	55	2.1	3,200	0	+	+	Achromia marked
							2/16/18	..	4.5	2,400	0	+	+	
							3/25/18	55	...	2,500	1	0	+	One megaloblast seen
13.6	3.67	271	153	0.74	43.2	—10#	3/30/18	65	...	1,800	0	0	+	Polychromatophilia not pronounced in this case
14.2	4.18	294	181	0.78	51.9	+ 9								
14.0	4.05	290	167	0.76	47.6	— 1‖								

* The two periods disagreed by 4 per cent.
# The two periods disagreed by 4 per cent.
‖ The two periods disagreed by 7 per cent.

with the immediate gravity of the case. Indeed, with the exception of Numbers 4, 9 and 12, the most severe cases were those who showed a metabolism beyond normal limits in either direction. In general, these severe types followed the order that the long standing, chronic cases gave a diminished, and the recent more acute ones, an elevated metab-

olism. It should be noted, however, that of those with a calorific output above normal, two patients (Numbers 15 and 18) had distinctly elevated temperatures, which would suggest that the increased metabolism was attributable, in part at least, to some influence other than the anemia. Two others (Numbers 16 and 17) of those with an increased energy output showed complications in the larger organs. Besides this coincidence between the intensity of metabolism and the duration of the disease, there is a certain parallelism to be seen between

TABLE 3.—Admission and End Data on—

Case No. and Name	Med. No.	Diagnosis	Sex	Age	Treatment		Metabolism					
					Description	Dates Metabolism and Treatment	Height, Cm.	Weight, Kg.	Buccal Temperature, F.	Pulse	Respiration
2 L. A. T.	7793 8298	Pernicious anemia; chronic type; duration, August, 1916 to January, 1918; remission, September, 1917 to November, 1917	♂	46	700 c.c. washed R.B.C. in physiol. saline 700 c.e. washed R.B.C. in physiol. saline 700 c.e. washed R.B.C. in physiol. saline 700 c.e. washed R.B.C. in physiol. saline	1/ 4/18 1/ 8/18 3/16/18 3/17/18 3/18/18	173.2	70.7 68.5	98.6 98.0	67 71	9.3 19.7
10 A. S.	7470 7669*	Splenic anemia; splenomegaly; duration of anemia, October, 1916 to October, 1917; progressing slowly and without remission	♀	18	..... Splenectomy.....	11/10/17 11/13/17 12/11/17	160.2	48.3 44.8	98.6 98.4	61 60	19.1 20.6
19 L. T. S.	7434	Pernicious anemia; lateral sclerosis; chronic type; duration of anemia, July, 1916 to October, 1917; no remissions	♀	40	250 c.c. citrated whole blood.....	10/26/17 10/31/17	..... 157.5	..... 56.6	..... 98.2	.. 69	.... 12.0
20 H. A. C.	7951	Secondary anemia; hemophilia; had had many attacks of bleeding but was well and at heavy work before the present hemorrhage	♂	52	650 c.c. citrated whole blood.....	1/15/18 2/ 6/18	..... 178.8	..... 66.7	..... 98.2	.. 68	.... 11.3
21 C. F. W.	8562	Pernicious anemia; chronic type; duration, January, 1917 to April, 1918; no remissions	♂	58	900 c.c. washed R.B.C. in physiol. saline	4/25/18 4/26/18	..... 184.4	..... 63.5	..... 98.0	.. 65	.... 14.1
22 G. A. C.	7527	Secondary anemia; pericarditis; pleurisy; peritonsillar abscess; duration of anemia about eight months	♂	39	550 c.c. washed R.B.C. in physiol. saline	1/ 5/18 1/ 8/18	..... 172.2	..... 53.1	..... 99.2	.. 78	.... 13.5
16 A. J .C.	7409	Splenic anemia; splenomegaly; duration of anemia, September, 1917 to October, 1917	♀	60	..... 117 millicuries radium applied to spleen 24 hours	10/23/17 10/28/17 10/30/17	157.0	56.6 55.8	98.8 99.2	97 90	14.8 14.3

* Surgical number.

pulse and metabolism. The abnormality of the metabolism, however, is far more marked than that of the pulse.

Tables 2 and 3, in contrast to Table 1, present a decidedly consistent picture. Most striking is the effect found as the result of treatment in all except three cases (Numbers 2, 3 and 16). Not only did the metabolism invariably fall, but, with the exception of Case 15, it reached a level either on the lower limit of or below normal. And this new level tended to hold despite further transfusions, and to repeat itself when a similar course of treatment was instituted in any later relapse. Parallel with this diminution in metabolism was a drop

in the pulse, in the respiratory activity as represented by the minute volume, and in the temperature if it had previously been elevated. The respiratory quotient was higher and, as was natural after transfusion, the simple cell count and the percentage hemoglobin were increased.

Of these changes following on treatment, the metabolism alone was of slow response. While the pulse and respiratory activity, the temperature and the blood picture reacted at once, or at least within

—Cases Studied During Treatment

Metabolism						Blood Picture							
Volume per Minute, L.	Volume per Respiration, C.c.	Oxygen Consumption per Minute, C.c.	Respiratory Quotient	Total Calories per Hour	Per Cent. Divergence from Aver. Normal Basal Linear	Date	Hemoglobin, per Cent.	R. B. C., Million	W. B. C.	Nucleated R.C.	Anisocytosis	Poikilocytosis	Remarks
4.31	463	215	0.78	61.5	—13	1/ 3/18	60	2.3	6,000	0	++	++	Few polychromatophilic and stippled cells seen
						3/18/18	55	2.3	4,800	0	++	0	Many macrocytes. No stippling
4.94	460	208	0.80	60.0	—15								
5.22	281	209	0.73	59.1	+ 5	11/ 8/17	68	3.0	4,800	0	0	0	Slight achromia
						12/ 8/17	75	4.4	12.000	0	0	0	
4.55	222	159	0.88	46.5	—15†								
....	....	....	....	....	....	10/29/17	68	2.2	4,200	0	+	+	Moderate polychromatophilia on Oct. 24, 1917
4.15	307	172	0.75	48.7	—14								
....	....	....	....	....	....	2/ 7/18	55	2.8	5,400	0	+	+	Marked achromia
5.32	501	210	0.84	61.1	—12								
....	....	....	....	....	....	4/26/18	90	3.0	2,300	0	+	+	
5.59	397	228	0.76	65.1	— 6								
....	....	....	....	....	....	1/ 5/18	53	1.9	10,000	0	+	+	A case of chronic sepsis with constant slight evening rise in temperature
4.92	364	225	0.71	63.2	— 2								
5.42	376	217	0.75	61.5	+15‡	10/22/17	68	3.6	7,000	0	+	+	Moderate polychromatophilia
5.38	372	212	0.76	60.4	+15								

† The two periods disagreed by 4 per cent.
‡ The two periods disagreed by 6 per cent.

twelve hours, the maximum effect on the metabolism seemed to take place only after a few days.

A discussion of the six cases reported in Table 2 will best show the facts as summarized in the foregoing.

Case 1 is of peculiar interest as representing chronic pernicious anemia of long duration. A hospital report shows this patient to have had a metabolism of minus 7 per cent. in 1916 (a year prior to the determination we have recorded). While his pulse and minute volume diminished soon after transfusion, it was not until some days later

that his heat output showed any change. It then seemed to have reached the true and remarkably low level at which it held.

Case 3 was likewise one of chronic anemia. This patient, however, as noted before, showed no metabolic response to transfusion. Her pulse, respiratory activity and respiratory quotient reacted in the general way, as did also her subjective symptoms. Of the last, the increased power to take food is especially worthy of mention. It may possibly be that this improved absorption of nutriment on the part of a person who had been using a decidedly subnormal amount of food masked what would otherwise have shown as a decreased metabolism.

Case 12, also one of long standing anemia, was carried through two periods of transfusion and moderate improvement, with an intervening relapse. Here the pulse rose after the first transfusion, but later pulse, metabolism, and respiration showed the usual diminution. At the end of each course of treatment the basal heat output showed the same level. Here, as in Case 1, this metabolic response to transfusion occurred only after a few days (compare the determinations of January 9 and 16, and of February 26 and 28), while the pulse and respiration dropped within twelve hours.

Case 14, under spontaneous improvement in a secondary anemia, showed the same type of changes, even to the blood picture, as occurred in all the cases after transfusion. Transfusion in this instance merely hastened the normal process of regeneration. In other words, natural improvement of the blood composition in anemia, as well as artificial improvement by transfusion, at first suppresses the stimulus acting on the body cells. This seems true no matter what the initial metabolism.

Case 15 represents a type diametrically opposite to Case 1. The onset of the disease was recent, the temperature before treatment was high, the metabolism and pulse elevated, the subjective symptoms grave. The response to transfusion, both metabolically and symptomatically, was marked, but of comparatively short duration. The cause of the disease was active, and the original symptoms soon reappeared, to subside once again to the same level as after the first series of transfusions. Even here, in an acute febrile case, responding to transfusion almost instantaneously in all other ways, the pronounced effect on the metabolism occurred only after an interval of a few days. (Compare date of April 5 and 9.) Likewise transfusion beyond a certain point had no effect on the energy requirement. (Compare the date of March 15, 20 and 25.)

What was stated for Case 15 may be practically repeated for Case 18. The patient here was dangerously ill and in the terminal stage of the disease. The metabolic level of the former was slightly lower, but otherwise the two patients presented very similar symptoms and reactions.

From the fact that the metabolism always falls after transfusion, no matter what its initial relation to normality, that this drop is preceded over a considerable interval of time by a fall in the pulse and respiratory activity, that the energy output seems to find a constant level beyond which it shows no further diminution, and that this level is either below or on the lower limit of normal — from these facts we feel that *two opposing factors, outside of any muscular activity, exert an influence on the metabolism of the anemic individual.*

First, there is a stimulus to the cells — perhaps only to certain ones such as those of the blood producing organs. The extent of this stimulus is expressed in the diminution of the metabolism which follows on transfusion. It is lost slowly as the cells readjust themselves to blood of more normal composition. Hence, the time interval between the introduction of blood into the body and the energy response of the organism.

Secondly, there is the opposing factor to the increased metabolism — namely, the tissue alterations attendant on the disease. The pathologic result of any anemia, and particularly of pernicious anemia, is replacement of normally active tissue by fat and water. In chronic pernicious anemia this replacement may reach an extreme degree, and expresses itself by the diminished heat output found in typical chronic cases and by the apparent tendency of all the cases to show a low metabolic level after transfusion when the stimulating factor has subsided.

The amount by which the metabolism falls after transfusion shows the strength of the stimulus exerted on the body cells, possibly for the purpose of blood production. And the level to which the metabolism falls shows the true bodily condition of the patient. A chronic case may thus be expected to reveal a decidedly lowered energy output, while from a recent case, where tissue compensation had not yet become an active factor, one may look for a practically normal calorific requirement. In our opinion, transfusion is a measure by which early cases of pernicious anemia may be assisted toward a remission and may be saved some degree of the fatty replacement of active tissue which in the end reduces them to a condition of sluggishness somewhat comparable to that seen in myxedema. If the case simply has a long history, the whole story is not told, since what is of importance is the length of the anemic periods and the possibility for bodily change which they present.

As a result of the work we have reported our course of action is now as follows: A typical case of pernicious anemia is admitted to the ward. After several days rest in bed, if food is being taken well

and if the temperature has become normal, a metabolism determination is carried out. Let us suppose the result is minus 10. In such an instance transfusion may result in a certain amount of immediate comfort, but there is little probability it will do more. The case is a chronic one in terms of the patient's actual physiologic condition. If the result is plus 10, transfusion is worth while. Such a result, a plus determination, will be given in persistently febrile cases on the first trial, and if as a consequence of transfusion the fever disappears and subsequent determinations give a pronounced minus value, again we can feel that further transfusion holds little in store. On the other hand, if the reduction in metabolism does not fall below normal either as a result of rest in bed or the first transfusion, the individual is one who has not progressed far in the disease, and transfusions should be pushed. While a course of transfusions does not prevent the development and progress of neurologic lesions, it does postpone the muscular sluggishness, which eventually reduces the chronic case of pernicious anemia to the state of a helpless burden.

CONCLUSIONS

1. Transfusion in cases of anemia produced the following results:
   a. a diminution of metabolism;
   b. a diminution of pulse and respiratory activity;
   c. a drop in temperature if it had previously been elevated;
   d. a rise in percentage hemoglobin and in the simple blood count.

2. The response of the metabolism to transfusion lags behind that of all the other factors by an interval of several days.

3. The lowering of metabolism is, therefore, not due simply to a cessation of the compensatory muscular activity of the anemic individual.

4. Before treatment the metabolism may be within normal limits or it may be above or below normal.

5. After transfusion the metabolism always reaches a normal or diminished level.

These facts suggest that the metabolism of the anemic individual is dependent on two contending factors, outside of any effects from compensatory muscular activity.

1. In untreated acute cases there is evidently some type of stimulation to the body cells in general and the amount of this stimulation is represented by the fall in metabolism after transfusion.

2. There are coincident progressive tissue alterations which tend to reduce metabolism. These alterations are represented by the diminished metabolism of the chronic cases, and by the low level to which the metabolism falls in practically all cases as a result of transfusion.

STUDIES ON ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA *

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In 1647 Thomas Willis recognized the presence of sugar by its sweet taste in the urine of diabetics. This sugar was identified as glucose by Chevreul in 1815. That diabetic blood also contained sugar was first recognized by Dobson in 1775, and his observation was confirmed the following year by Cullen.[1]

In 1831 Tiedemann and Gmelin[2] showed that sugar was normally present in the blood after meals, and that it originated in the digestion of starchy food in the intestine. Up to this time sugar had been considered a pathologic product in the blood and urine of diabetics. The fact that sugar is present in the blood of an animal on a carbohydrate-free diet was first demonstrated by Claude Bernard in 1848. Eight years later, Chauveau asserted that sugar was a constant constituent of the blood, that its presence was not dependent on the diet, and that in the fasting state the sugar value remained constant. The dependence of glycosuria on hyperglycemia was recognized at this time following the work of MacGregor, Rollo and Ambrosini, and tests for the assimilation limit for glucose and starch were instituted by C. Schmidt, v. Becker, Schiff, Lehmann, Frerichs and others, the urine being tested for sugar. This assimilation-limit for glucose has been found to be not at all constant, varying in different individuals and in the same individual, being greatly lowered by starvation as shown by Hofmeister.[3] The method usually employed was to give from 50 to 200 gm. of glucose to an individual of average weight, and to test the urine at intervals for the presence of sugar. The normal values given by different authors vary from 50 to 200 gm. In many cases the urine was examined at intervals varying from one to twenty-four hours after the ingestion of the sugar, and this, with inaccurate methods of sugar determination, largely explains the discrepancies. Other sources of error are the state of health, nutrition and body weight of the patient. The advent of practical methods of blood analysis directed the attention of investigators to tests of alimentary hyperglycemia and the determination of the patient's toler-

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1. Bernard, Claude: Compt. rend de l'acad. d. sc., 1876, p. 1405
2 Tiedemann and Gmelin: Die Verdaung nach Versuchen, Heidelberg, 1831.
3. Hofmeister: Arch. f. exper. Path. u. Pharmakol. **26**:355, 1891.

ance for glucose in this way. Results of such tests have been published by Liefmann and Stern,[4] Boudouin,[5] Frank,[6] Wacker,[7] Tachau,[8] Jacobson,[9] Bergmark,[10] Hopkins,[11] Cummings and Piness,[12] Hamman and Hirschman,[13] Denis and Aub[14] and others. In many of these tests the estimations were made one and two hours after the ingestion of glucose, and the results compared with the preformed sugar value. In other cases the test was more elaborate, the blood being examined at frequent intervals for a period of from four to six hours. These observers seem to agree that in a normal person, following the ingestion of sugar, the blood sugar reaches its greatest concentration in from one-half to one hour, and that the normal value is again reached

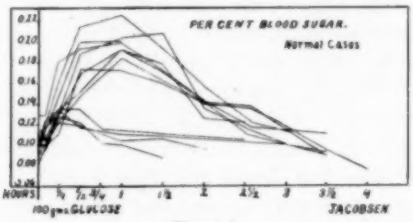

Chart 1

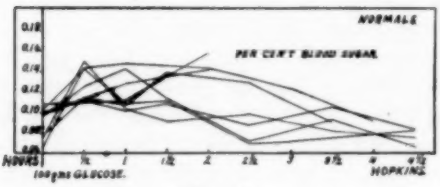

Chart 2

in from two to three hours' time. There is no agreement as to the height of the hyperglycemia. Great variations are to be expected. Aside from the inaccuracies of the various methods we have the uncertain factors of intestinal absorption, state of nutrition, weight of the subject, glycogenetic and glycolytic powers, renal permeability, and glycolysis in the intestine and in the withdrawn blood before the test

4. Liefmann and Stern: Biochem. Ztschr. **1**:299, 1906.
5. Boudouin: Thése de Paris, 1908.
6. Frank: Ztschr. f. physiol. Chem. **70**:291, 1910.
7. Wacker: Ztschr. f. physiol. Chem. **67**:197, 1910.
8. Tachau: Arch. f. klin. Med. **104**:437, 1911.
9. Jacobsen: Biochem. Ztschr. **56**:471, 1913.
10. Bergmark: Jahrb. f. Kinderh. **80**:373, 1914.
11. Hopkins, A. H.: Am. J. M. Sc. **149**:254, 1915.
12. Cumings and Piness: Arch. Int. Med. **19**:777, 1917.
13. Hamman and Hirschman: Arch. Int. Med. **20**:761, 1917.
14. Denis and Aub: Arch. Int. Med. **20**:964, 1917.

is carried out. Illustrating these agreements and variations, composite charts (Charts 1, 2 and 3) made from figures published by Jacobsen,[9] Hopkins,[11] and Hamman and Hirschman[13] are given.

A combination of blood and urine analyses following the ingestion of glucose has been found more instructive. In the fourteen normal cases reported by Jacobsen[9] (Chart 1) sugar was found in the urine in all those whose blood sugar reached a value of 0.174 per cent.; in those below 0.16 per cent. sugar was not found in the urine. Jacobsen's work shows the fallacy of blood analyses at one-hour intervals, as in many normal cases following the ingestion of 100 gm. of glucose, hyperglycemia had already passed off by the end of the first hour.

Bailey[15] reported a normal case on whom frequent blood and urine sugar tests were made following the ingestion of 75 gm. of glucose. The type of blood sugar curve was similar to those of Jacobsen[9] and, as in his cases, the kidneys actively excreted sugar after a concentration of 0.167 per cent. had been reached in the blood.

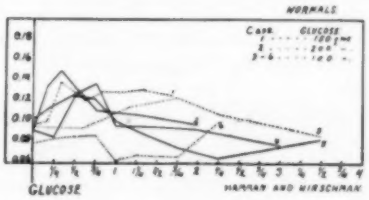

Chart 3

Hamman and Hirschman[13] carried out similar tests on six normal persons, using from 100 to 200 gm. of glucose. In three of their cases the blood sugar curve was of a similar type to those of Jacobsen; the others were very irregular (Chart 3). In these cases active renal excretion of sugar began at blood sugar concentrations varying from 0.124 to 0.255 per cent., giving an average of 0.17 per cent.

An important observation on all of these tests is the marked disproportion between the greatest blood sugar concentration and the amount of sugar ingested, allowances being made for differences in body weight. This disproportion is seen in the work of individual authors and makes one think that sugar tolerance tests based on blood sugar estimations are really tests of intestinal absorption.

15. Bailey, C. V.: Proc. Soc. Exper. Biol and Med. **13**:153, 1916.

TESTS OF ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA

Stimulated by the works of Bang,[16] Jacobsen,[9] and Hopkins,[11] the present work was undertaken in an attempt to show the relation of glycosuria to hyperglycemia as found in health and as influenced by disease. It was hoped that in such tests interesting observations could be made on variations in blood volume, on the rate of sugar increase in corpuscles as compared to that in the plasma, and on the influence of urine excretion on glycosuria.

METHOD OF PROCEDURE

The subjects partook of a light meal at 5:30 on the afternoon preceding the tests. On the following morning the experiment was begun before anything had been eaten or drunk. The bladder was emptied and later a specimen of urine was passed on which was determined the rate of urinary excretion and the presence or absence of sugar. A specimen of blood was obtained at this time by venipuncture. Following this a certain amount of glucose in a known volume of weak tea was given by mouth and blood and urine specimens obtained at frequent intervals for a period of six or seven hours. In some cases fluid was given during this period. The subject was kept quiet in a reclining posture throughout. Urine sugar tests were made qualitatively by Benedict's method;[17] quantitatively by Benedict's or Myers'[18] methods and by means of the polariscope. In some cases the sugar was determined to be glucose by the character of its osazone.

Blood sugar was estimated by a modification of the Lewis and Benedict[19] method.

Hemoglobin tests were made with the Hellige colorimeter.

Plasma volume was determined by centrifuging the blood in graduated tubes. Chlorids in the urine were estimated by the Volhard-Harvey method. Sugar estimations were made on unwashed corpuscles from which the plasma and upper layers of cells had been pipetted off leaving a known volume of cells in the centrifuge tube.

The data from these last estimations unfortunately do not give one a correct idea of the relative glucose increase in corpuscles and plasma, as by this method a half hour elapsed before the plasma and corpuscles were separated. This gave time for absorption by the corpuscles and a more even distribution of the glucose. The data are, however, of value in showing the distribution of glucose in blood, in which the glucose concentration is not changing. Gradwohl and Blavis,[20] who, by the way, were student and technician, respectively, in the laboratory where this work was being done, have published results similar to these now reported.

16. Bang, I.: Der Blutzucker, Wiesbaden, 1913.
17. Benedict, S. R.: J. Biol. Chem. **5**:485, 1909; **9**:57, 1911.
18. Myers, V. C.: Proc. Soc. Exper. Biol. and Med. **13**:178. 1916.
19. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147, 1915.
20. Gradwohl and Blavis: J. Lab. & Clin. M. **2**:416, 1916-1917.

Alimentary Glucose Test in a Normal Person

CASE 1.—S. S., male, aged 18, was admitted to hospital for observation as a suspected case of pulmonary tuberculosis. Aside from being poorly nourished, nothing abnormal was found on physical examination. His morning blood sugar on two occasions was 0.1 and 0.11 per cent. On the morning of May 15, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 4 and Table 1. The patient was quite nervous at the beginning of the test, and this probably accounts for the preformed sugar being higher than on previous occasions. The urine sugar was slightly lower than the synchronous blood sugar. Following the administration of the glucose, the blood and urine sugar increased at the same rate up to a concentration of 0.167 per cent., when the urine sugar increased rapidly to 0.89 per cent., although the blood sugar at this time had reached only 0.22 per cent. The blood sugar curve is of the same type as found in normals by Jacobsen and others. The urine sugar value returned to normal more slowly than the blood sugar. Following the ingestion of glucose the blood volume (as shown by the estimation of hemoglobin) increased 7 per cent. during the first half hour, returning to normal in one and one-half hours, although the blood sugar at this time was concentrated. Epstein[21] has frequently referred to this volume increase. The rate of urinary excretion decreased notwithstanding the fact that 400 c.c. of fluid were taken with the glucose. Not before the blood sugar had reached its highest level and was on the decline, did the rate of urinary excretion increase.

TABLE 1 (CASE 1, S. S., 5/15/16).—ALIMENTARY GLUCOSE TEST IN A NORMAL PERSON

Time		Blood					Urine				Fluid Intake, C.c.
				Sugar				Sugar			
								Myers Method		Benedict's Method, Qualitative	
A. M.	Hr.	Hemoglobin, Units	Plasma, per Cent.	In Whole Blood, per Cent.	In Plasma, per Cent.	In Corpuscles, per Cent.	C.c. per Hour	Per Cent.	Gm. per Hour		
9:10	...	80	45.5	0.12	0.118	0.121	36.0	0.099	0.035	0	400
9:15	75 gm. glucose			.....	.....	.....	....	.....	....	....	
9:30	¼	77	44.5	0.153	0.127	0.132	28.2	0.171	0.048	0	
9:50	½+	73	46.3	0.172	0.19	0.154					
10:10											
10:15	1	77	46.0	0.22	0.225	0.193	31.2	0.891	0.28	++++	
10:40	1½—	80	45.3	0.216	0.22	0.211					
11:00											
11:15	2	78	47.0	0.158	0.147	0.147	31.8	0.405	0.129	+++	
11:30											
11:45	2½	79	46.0	0.147	0.147	0.147	16.8	0.315	0.053	++	
12:00 M.											
P. M.											
12:15	3	78	47.0	0.134	0.113	0.124	22.8	0.27	0.06	+	
1:00	3¾	78	46.5	0.135	0.121	0.124					
1:45	4½	76	45.5	0.129	0.121	0.113	21.0	0.252	0.053	+	
2:00											
2:15	5	77	42.0	0.129	0.126	0.113	22.8	0.162	0.037	0	
3:15	6	78	40.0	0.087	0.085	0.091					

This experiment seems to indicate that a normal person, when uninfluenced by food or fluid intake, has reducing substances present in equal concentration in both blood and urine. Following the inges-

21. Epstein, A. A.: Studies on Hyperglycemia in Relation to Glycosuria, New York, 1916.

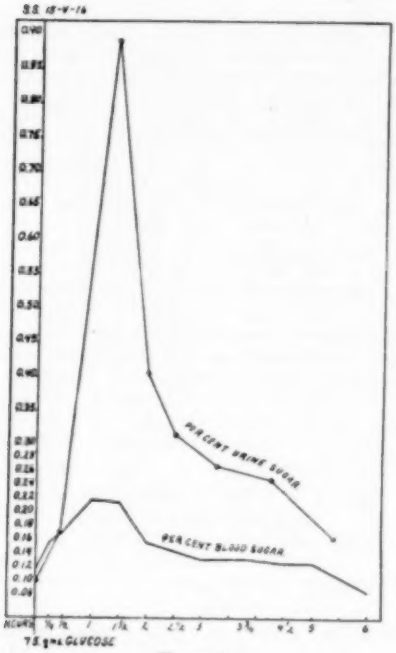

Chart 4

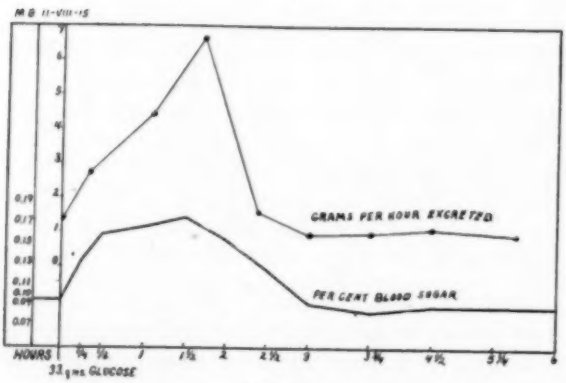

Chart 5

tion of glucose, urine sugar parallels that of the blood up to the latter's concentration of 0.16 to 0.17 per cent. As the blood sugar increases beyond this point the kidneys actively excrete sugar. This excessive excretion decreases as the hyperglycemia passes off. There seems to be an attempt to control the blood sugar concentration by an increase in blood volume. This is partly brought about by a decrease in urinary excretion.

A comparison of the hyperglycemic curves in plasma and corpuscles indicates a more rapid rise in plasma than corpuscles. (This difference, however, is probably much greater than the figures show. As before stated, a half hour elapsed before plasma and corpuscles were separated, giving time for an even distribution of the glucose.)

The findings in this case emphasize the necessity of adopting Benedict's term "glycuresis" [22] to indicate active excretion of sugar in contradistinction to the amount found in the urine during the fasting state.

TABLE 2 (CASE 2, M. B., 8/11/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF RENAL DIABETES

Time		Blood Sugar, per Cent.	Urine				Fluid Intake, C.c.
			C.c. per Hour	Chlorids, Gm. per Hour	Sugar		
A. M.	Hr.				Per Cent.	Gm. per Hour	
9:15	...	0.098	60.0	0.046	3.12	2.0	
9:45	33 gm. glucose		44.0	.....	2.94	1.29	225
10:00	¼	0.135					
10:20	½	0.159	58.0	0.1056	4.83	2.83	225
10:30							
10:45	1	0.168	....	.....	....	.....	225
11:00	1¼	0.172	66.0	0.145	6.66	4.398	
11:10							
11:15	1½	0.176					
11:45	2	0.156	97.0	0.218	6.75	6.7	225
P. M.							
12:15	2½	0.105					
			159.0	0.254	1.04	1.65	
12:25							
12:45	3	0.093					
			94.0	0.169	0.952	0.897	
1:00							
1:25	3½	0.086					
1:45	4	0.088	150.0	0.21	0.657	0.986	225
2:00							
2:15	4½	0.092					
			90.0	0.14	1.2190	1.097	
3:00	5¼	0.092	.....	.....	.....	.....	225
3:45	6	0.092	84.0	0.134	1.086	0.912	

Alimentary Glucose Test in a Case of "Renal Diabetes" [23]

CASE 2.—M. B., female, aged 31, had persistent glycosuria for at least ten years, resisting repeated attempts at treatment; no symptoms of diabetes. For many years her only complaint had been lack of reserve energy. Restriction of diet caused extreme weakness and rapid loss of weight. Her urine showed

22. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **34**:258, 1918.

23. For further discussion of renal diabetes see Bailey, C. N.: Am. J. M. Sc. **157**:221, 1919.

a trace of protein and a few hyaline and granular casts. Blood pressure: systolic, 110; diastolic, 65.

On the morning of Aug. 5, 1915, her blood sugar was 0.09 per cent., the synchronous urine sugar being 1 per cent. Two days later, with a blood sugar of 0.11 per cent., the urine contained 1.6 per cent. sugar. August 11, she was tested with 33 gm. of glucose. The results are shown in Chart 5 and Table 2. (At this time the patient was four months' pregnant.)

One sees that the patient excreted sugar at the rate of 2 gm. per hour, although at this time her blood sugar was normal. The blood sugar curve is slightly delayed and prolonged. The excretion of sugar was excessive throughout. This being most marked at the 1½-hour period when sugar was being excreted at the rate of 6.7 gm. per hour, although the blood sugar was at about the concentration where normal kidneys become permeable.

The test was repeated fourteen months later. At this time the percentage of glucose in her daily urine had greatly increased, being 7.4 per cent. on Oct. 15, 1916, 6.94 per cent. on the 16th and 9.2 per cent. on the 17th. The glucose test was repeated October 13. The results are shown in Chart 6 and Table 3.

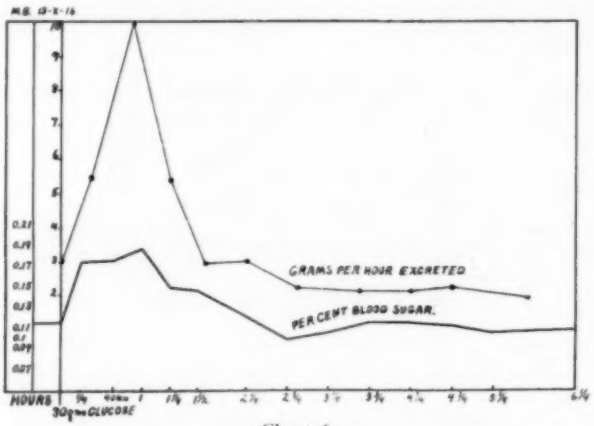

Chart 6

In this test the blood sugar value was within normal limits, but sugar was being excreted at 2.98 gm. per hour. The blood sugar curve is of the normal type. With a blood sugar of 0.189 per cent., sugar was being excreted at the rate of 9.9 gm. per hour. If we compare this test with the previous one (made when the patient was four months pregnant) we find that the blood sugar in the fasting state had increased in value. This, however, is explained by the first test having been made after three days' fasting, which lowers the value. The latter test was made after a ten-hour fast.

The excretory power of the kidneys had increased and the more rapid rise in blood sugar probably indicates an increased absorptive power of the intestines. In the first test the slight delay and prolongation of hyperglycemia is possibly due to slight embarrasment of the kidneys at that time.

In Table 3, the estimation of hemoglobin indicates a 6 per cent. increase in blood volume during the development of the hyperglycemia. The volume returned to normal with the blood sugar. The rate of urinary excretion fell off rapidly on the ingestion of glucose, notwithstanding the large fluid intake, and did not increase until the hyperglycemia had developed.

TABLE 3 (CASE 2, M. B., 10/13/16).—RESULTS OF SECOND GLUCOSE TEST

Time		Blood		Urine			Fluid Intake, C.c.
		Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Sugar		
A. M.	Hr.				Per Cent.	Gm. per Hour	
9:15	...	67	0.116	63.0	8.3	2.98	
9:30	30 gm. glucose		.....	....	...	....	400
9:45	¼	62	0.177	36.0	11.9	5.35	
10:10	¾	61	0.177				
10:30	1	62	0.189	45.0	3.0	9.9	
10:40							
10:50	1¼	63	0.15	33.0	1.6	5.28	
11:00							
11:10	1¾	64	0.147	80.0	3.7	2.96	
11:30							
11:45	2¼	65	0.12	120.0	2.5	3.0	
12:00 M.							
P. M.							
12:15	2¾	65	0.10	37.0	6.2	2.31	
12:45	3¼	66	0.106				
1:15	3¾	67	0.116	56.0	5.6	2.09	
1:30							
1:45	4¼	67	0.114	36.0	6.0	2.16	
2:00							
2:15	4¾	67	0.112	34.0	6.5	2.21	
2:30							
2:45	5¼	68	0.106	28.0	6.8	1.9	
3:30							
3:45	6¼	68	0.108				

Alimentary Glucose Test in a Case of Early Mild Diabetes

CASE 3.—J. S. B., male, aged 42. Sugar was accidentally discovered in his urine during a routine military examination. He was apparently in excellent health, but had noticed slight polydipsia, polyuria and polyphagia. Sugar was constantly present in the daily urine, but hourly specimens showed that it was excreted only after meals. His morning blood sugar on several examinations was about 0.1 per cent. and at these times his urine was sugar-free.

March 3, 1916, he was tested with 60 gm. of glucose. The results are shown in Chart 7 and Table 4. (One hour before the test the patient negligently drank a cup of sweetened coffee which accounts for the high preformed blood sugar value.) The blood sugar curve rises a little more rapidly than normal, but otherwise is of the latter type. The excretion of sugar is excessive and follows the increase of blood sugar. At the 5½ and 6¼-hour periods one can determine that the kidneys actively excrete glucose between blood sugar concentrations of 0.123 and 0.126 per cent., which is much lower than normal.

On Jan. 24, 1917, the test was repeated, using 33 gm. of glucose. The results are shown in Chart 8 and Table 5. The blood sugar is of normal value. The blood sugar curve again rises and falls rapidly. Glucose excretion is excessive and appears at a lower blood sugar concentration than normal.

TABLE 4 (CASE 3, J. S. B., 3/3/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF EARLY MILD DIABETES

Time		Blood					Urine					Fluid Intake, C.c.
					Sugar				Sugar		Chlorids, Gm. per Hour	
A. M.	Hr.	Hemoglobin, Units	Cells, per Cent.	Plasma, per Cent.	In Whole Blood, per Cent.	In Plasma, per Cent.	C.c. per Hour	Sp. Gr.	Per Cent.	Gm. per Hour		
10:10	...	84.0	61	39	0.15	0.136	96.0	1.030	0.2	0.19	1.45	
10:15	60 gm. glucose	..	..	.....	.....	....	.....	...	....	....	300	
10:30	¼	82.0	61	39	0.205	0.192	54.0	1.031	3.1	0.17	0.62	
10:45	½	80.5	58	42	0.228	0.216						
10:55												
11:00	¾	82.0	62	38	0.228	0.216	....	.....	...	....	....	300
11:15	1	83.0	63	37	0.216	0.204	84.0	1.033	5.3	4.45	0.7	
11:40												
11:45	1½	82.0	62	38	0.185	0.156	78.0	1.035	4.6	3.59	0.81	
P. M.												
12:15	2	83.0	63	37	0.114	0.088						
12:45	2½	83.0	65	35	0.09	0.068	31.8	1.029	1.0	0.318	0.48	
1:35	...	....	..	..	....	.....	28.8	1.030	0.5	0.14	0.36	300
1:43	3½	83.0	65	35	0.12	0.10	....	.....	...	....	....	300
2:45	4½	83.0	60	40	0.12	0.11	78.0	1.017	0.0	0.0	0.2	
3:00												
3:45	5½	84.0	63	37	0.126	0.116	36.0	1.023	0.25	0.09	0.17	
4:00												
4:30	6¼	83.0	63	37	0.123	0.112	26.4	1.030	0.0	0.0	0.2	
4:45												

TABLE 5 (CASE 3, J. S. B., 1/24/17).—RESULTS OF SECOND TEST

Time		Blood Sugar per Cent.	Urine				Fluid Intake, C.c.
			C.c. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.				Per Cent.	Gm. per Hour	
9:45	...	0.104	44.4	1.023	0.0	0.0	
10:00	33 gm. glucose		....	.....	...	.....	400
10:15	¼	0.141	34.2	1.022	0.71	0.24	
10:30	½	0.138					
10:40							
10:45	¾	0.129					
11:00	1	0.108					
11:15	1¼	0.114					
			24.0	1.030	1.66	0.398	
11:30	1½	0.104					
11:45	1¾	0.09					
12:00 M.	2	0.10					
P. M.							
12:30	2½	0.098					
			18.0	1.031	0.3	0.054	
1:00	3	0.10					
1:30	3½	0.10					
2:30	4½	0.10	17.4	1.028	0.0	0.0	
3:00							

In these two tests the extent of the hyperglycemia seems to vary directly with the amount of sugar ingested.

In the first test the blood volume (as indicated by the hemoglobin) increased 3.5 per cent. during the increase in blood sugar, later returning to normal. Urinary excretion decreased following the ingestion of glucose.

Alimentary Glucose Test in a Case of Diabetes of Long Standing Without Kidney Involvement

CASE 4.—S. O., female, aged 65, had symptoms of diabetes for fourteen years. Treated indifferently for that period. At time of examination she suffered from neuralgia, weakness, polyuria, polydipsia, polyphagia, and pruritis. The urine contained 6 per cent. glucose in the twenty-four-hour specimen; no protein or casts. Blood pressure: systolic, 150; diastolic, 90. Her morning blood sugar was 0.23 and 0.225 per cent. on two occasions, the

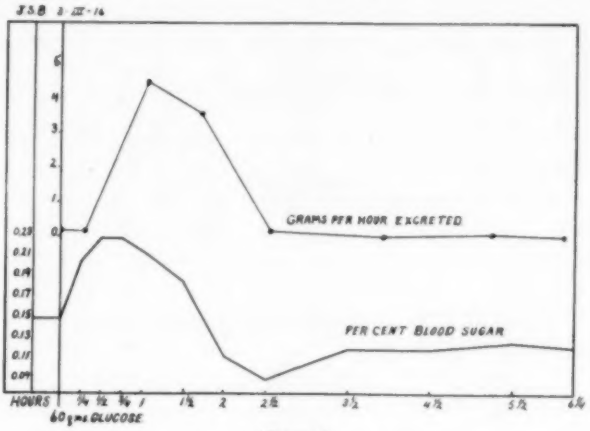

Chart 7

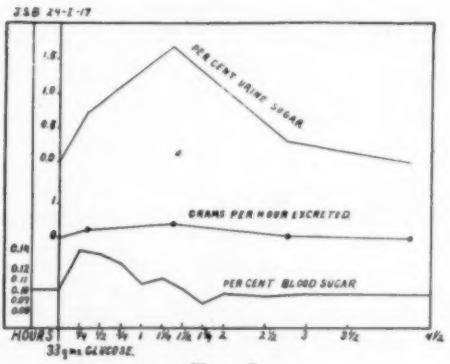

Chart 8

urine passed at the same period being free from sugar. Dec. 17, 1915, she was tested with 66 gm. of glucose. The results are shown in Chart 9 and Table 6. In this case the preformed sugar was high (0.22 per cent.), the blood sugar increased rapidly, reaching its highest point in three-quarters of an hour, and then quickly decreased. Unfortunately, specimens of blood could not be obtained after the 2¾-hour period. The urine at the beginning of the test was free from sugar.

TABLE 6 (CASE 4, S. O., 12/15/17).—ALIMENTARY GLUCOSE TEST ON A CASE OF DIABETES WITHOUT KIDNEY INVOLVEMENT

Time		Blood		Urine				Fluid Intake, C.c.
		Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.					Per Cent.	Gm. per Hour	
9:45*	...	69	0.22	33.6	1.019	0.0	0.0	
10:00	66 gm. glucose		.....	.....	.....	...	....	600
				30.0	1.025	0.2	0.06	
10:15	¼	69	0.384					
10:30	½	68	0.432	147.6	1.026	3.1	4.57	
10:45	¾	68	0.492					
11:00	1	68	0.49					
11:15	1¼	68	0.472	210.0	1.025	4.9	10.29	
11:30	1½	68	0.448					
				150.0	1.030	6.5	9.75	
11:45	1¾	68						
12:00 M.								
P. M.								
12:15	2¼	69	0.36	129.6	1.032	6.2	8.03	
12:30								
12:45	2¾	69	0.32	60.0	1.031	5.3	3.18	
1:00	...	..	.....	33.6	1.020	4.6	1.54	250
1:30	...	..	.....	48.0	1.015	0.1	0.04	
2:10	...	..	.....	154.2	1.005	0.0	0.0	

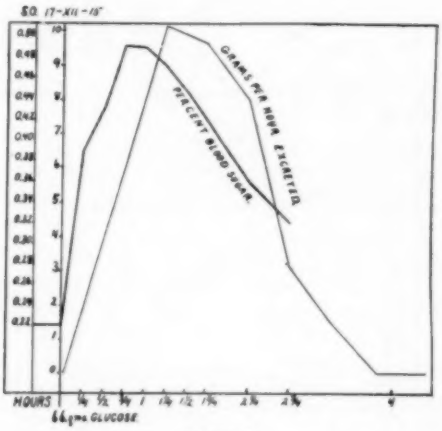

Chart 9

One cannot determine at what blood sugar concentration the kidneys actively excreted glucose, but it was between 0.22 and 0.384 per cent. The excretion of sugar was marked; it followed the blood sugar curve, and could no longer be detected with Benedict's solution at the end of four hours' time. Urine excretion decreased in the first quarter of an hour, later being uninfluenced by the increasing blood sugar. The blood volume (indicated by hemoglobin) was but slightly affected, increasing 1 per cent. This is due to the rapid response of the kidneys to fluid intake.

ALIMENTARY HYPERGLYCEMIA IN DIABETES

Alimentary hyperglycemia in diabetes, following the ingestion of glucose, has been frequently studied. Hopkins[11] examined nine cases and found a high preformed blood sugar value. Following the administration of 100 gm. of glucose there was a markedly prolonged hyperglycemia. Similar results have been found by Epstein,[21] Hamman and Hirschman,[13] and Cummings and Piness.[12] Chart 10 is a composite from tests made by Epstein on cases of diabetes without renal involvement; Chart 11 from tests made by the same author in cases

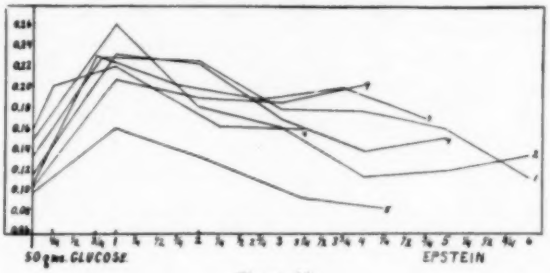

Chart 10

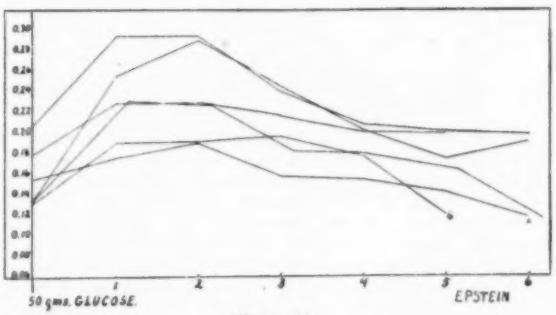

Chart 11

of diabetes with renal involvement. The effect of the nephritis was to increase the preformed blood sugar value and to prolong the hyperglycemia.

Alimentary Glucose Test in a Case of Chronic Interstitial Nephritis

CASE 5.—V. A., male, aged 27, had hemorrhagic nephritis following erysipelas seven years previous to admission. Frequent repeated attacks of great severity. At present, cardiac and vascular hypertrophy, retinitis; blood pressure: systolic, 235; diastolic, 160. Urine, 1,500 c.c.: specific gravity, 1.010; protein, moderate amount; an occasional granular cast; no sugar. Phenol-

sulphonephthalein excretion, 8 per cent. in two hours. Blood chemistry: sugar, 0.165 per cent.; uric acid, 10.5 mg. per 100 c.c.; creatinin, 8.3 mg. per 100 c.c.; urea nitrogen, 59 mg. per 100 c.c.; combines 50 c.c. carbon dioxid per 100 c.c. of plasma.

TABLE 7 (CASE 5, V. A., 11/18/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF CHRONIC INTERSTITIAL NEPHRITIS

Time		Blood			Urine				Fluid Intake, C.c.
			Sugar		C.c. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.	Hemoglobin, Units	In Whole Blood, per Cent.	In Plasma, per Cent.			Per Cent.	Gm. per Hour	
9:00	...	59	0.159	0.147	58.0	1.010	0.0	0.0	
9:15	75 gm. glucose	.....	.....	.....	....	.....	...	....	330
					45.0	1.014	0.0	0.0	
9:30	¼	57	0.188	0.172					
9:40									
9:45	½	56	0.252	0.234					
10:00	¾	57	0.287	0.266					
					30.0	1.012	+	....	240
10:20	1+	58	0.296	0.272					
10:30									
10:45	1½	58	0.369	0.351					
					54.0	1.022	0.5	0.27	220
11:15	2	59	0.342	0.36					
11:30									
11:45	2½	58	0.296	0.296	....	.....	...	....	220
					66.0	1.006	0.1	0.06	
P. M.									
12:20	3	59	0.228	0.222					
12:30									
1:15	4	59	0.156	0.15	54.6	1.014	+		
1:30	...	..	.....	.....	....	.....	...	....	450
2:00	...	..	.....	.....	56.4	1.014	0.0	0.0	
2:15	5	59	0.126	0.117	60.0	1.010	0.0	0.0	
3:10									
3:15	6	59	0.144	0.132	60.0	1.014	0.0	0.0	
									220
3.45									

Feb. 18, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 12, Table 7. The preformed sugar is high, as is found in nephritis. The kidneys become permeable to sugar between 0.25 and 0.3 per cent. blood sugar. The blood sugar curve is delayed and prolonged, the highest point being reached in one and one-half hours, and the patient's normal not being regained before the four-hour period. The excretion of sugar is very slight, 0.27 gm. per hour being excreted with a blood sugar of 0.369 per cent.

Hemoglobin estimations show a 3 per cent. increase, which slowly returns to normal with the blood sugar. The excretion of urine decreases during the development of the hyperglycemia.

ALIMENTARY HYPERGLYCEMIA IN NEPHRITIS

Alimentary hyperglycemia in nephritis has been studied by Neubauer,[24] Tachau,[25] Hopkins,[11] Epstein,[21] Hamman and Hirschman[13] and others, following the administration of glucose by mouth (usually 100 gm.). Chart 13 is a composite of the results of the test in four patients examined by Hopkins; Chart 14 is a composite of the six cases of Hamman and Hirschman. In all of these cases

24. Neubauer: Biochem. Ztschr. **25**:284, 1910.
25. Tachau: Deutsch. Arch. f. klin. Med. **104**:448, 1911.

the curve is similar to that found in many cases of diabetes and shows the fallacy of alimentary hyperglycemic tests alone as a diagnostic method. Especially is this true of the practice of testing the blood at one-hour intervals, for in nephritis, as well as in diabetes (with renal involvement), the second hour specimen is apt to contain as much or more glucose than the first hour specimen.

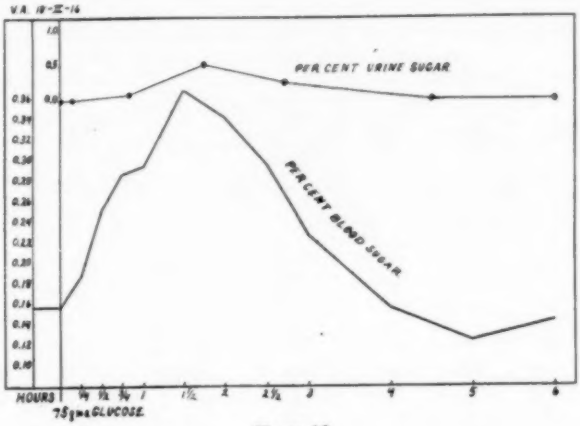

Chart 12

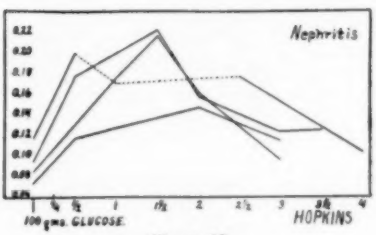

Chart 13

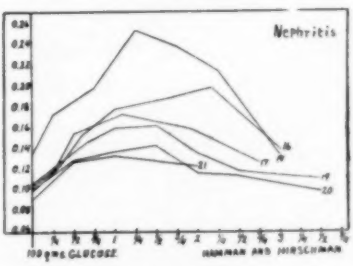

Chart 14

Alimentary Glucose Test in Diabetes with Renal Involvement

CASE 6.—C. M., male, aged 54. Glycosuria was discovered a few years prior to admission. The patient suffered from cardiac decompensation, dilatation, irregular pulse, edema, ascites, and dyspnea. The urine contained a moderate amount of protein and many hyaline and granular casts. Phenolsulphonephthalein excreted in two hours, 29 per cent. Blood pressure: systolic, 200; diastolic, 150. Blood chemistry: sugar, 0.21 per cent.; urea nitrogen, 16 mg. per 100 c.c. blood; uric acid, 3.6 mg. per 100 c.c. blood; creatinin, 2.9 mg. per 100 c.c. blood.

TABLE 8 (CASE 6, C. M., 12/9/15).—ALIMENTARY GLUCOSE TEST IN DIABETES WITH RENAL INVOLVEMENT

Time		Blood		Urine				Fluid Intake, C.c.
		Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.					Per Cent.	Gm. per Hour	
9:15	...	81.5	0.21	72	1.011	0.0	0.0	
9:30	33 gm. glucose	.....	.....	..	.....	...	....	250
9:45	¼	81.5	0.24	?	?	0.0	0.0	
10:00	½	77.0	0.288					
10:15	¾	78.0	0.306	48	1.015	++	?	
10:30	1	80.0	0.301					250
10:45	1¼	80.0	0.301	96	1.013	0.61	0.58	
10:50								250
11:15	1¾	81.0	0.252	114	1.010	0.153	0.17	
11:45	2¼	81.0	0.25	90	1.011	++	?	250
P. M.								
12:15	2¾	81.5	0.235	120	1.011	+	?	
12:45	3¼	81.5	0.23	204	1.008	0.0	0.0	
1:15	3¾	83.0	0.215	120	1.012	0.0	0.0	
1:45	4¼	82.0	0.210	102	1.010	0.0	0.0	
2:45	5¼	81.5	0.205	72	1.010	0.0	0.0	

Dec. 9, 1915, he was tested with 33 gm. of glucose. The results are shown in Chart 15 and Table 8. The striking features are the high preformed blood sugar value, the rapid rise in blood sugar, reaching its highest point in three-quarters of an hour, the great delay in returning to normal (four and one-fourth hours), and the very slight excretion of sugar.

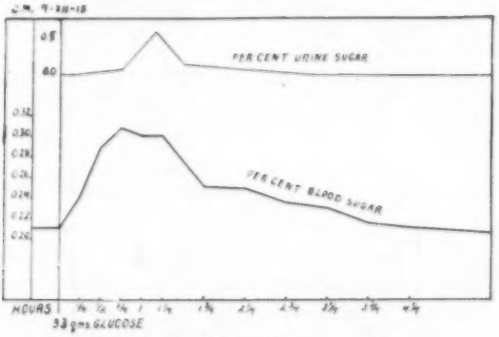

Chart 15

Blood volume increased 4.5 per cent. (as indicated by hemoglobin) during the hyperglycemia, later returning to normal. Urinary excretion fell off markedly, greatly increasing as the hyperglycemia subsided.

CASE 7.—I. A., female, aged 46. Diabetes eleven years. Chronic interstitial nephritis. Daily urine contained from 3 to 6 per cent. sugar on ordinary diet, a trace of albumin, and a few hyaline and granular casts. Blood chemistry: sugar, 0.26 per cent.; urea nitrogen, 30 mg. per 100 c.c. blood; uric acid, 6 mg. per 100 c.c. blood; creatinin, 3 mg. per 100 c.c. blood. Phenolsulphonephthalein, 52 per cent. excreted in two hours. Morning urine free from sugar.

TABLE 9 (CASE 7, I. A., 11/1/16).—DIABETES WITH RENAL INVOLVEMENT

Time		Blood		Urine						Fluid Intake, C.c.
					Sugar					
						Myers Method				
A. M.	Hr.	Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Benedict's Method, per Cent.	Per Cent.	Gm. per Hour	Chlorids, Gm. per Hour	Sp. Gr.	
9:15	...	67	0.255	36.0	0.125	0.12	0.043	0.201	1.018	400
9:30	30 gm. glucose	.....	.....	.....	.....	.....	.....	.....	.....	
				233.0	0.15	0.159	0.37	1.302	1.012	
9:45	¼	64	0.275							
10:00	½	64	0.352	258.0	0.72	0.54	1.39	0.516	1.010	
10:15	¾	61	0.424							
				468.0	1.4	1.08	5.05	0.748	1.008	
10:30	1	63	0.441							
10:45	1¼	64	0.459	420.0	1.58	1.41	5.92	0.714	1.010	
11:00	1½	64	0.459							
11:15	1¾	65	0.45	170.0	2.88	2.12	3.6	0.577	1.015	
11:30	2	66	0.441							
11:45	2¼	66	0.413							
12:00 M.	2½	67	0.392	117.0	2.76	2.35	2.75	0.444	1.019	
P. M.										
12:10										
12:30	3	66	0.364	94.0	2.58	2.0	1.87	0.374	1.020	
12:45										
1:00	3½	68	0.343	52.0	2.22	2.0	1.03	0.258	1.023	
1:15										
1:30	4	68	0.31	40.0	2.13	2.04	0.8	0.213	1.021	
2:00	4½	68	0.30							
2:30	5	68	0.29	38.0	1.68	1.47	0.55	0.226	1.025	
3:00	5½	69	0.275							
3:30	6	70	0.26	39.0	0.92	0.77	0.3	0.27	1.026	
4:00	6½	70	0.255							
4:30	7	70	0.24	39.0	0.92	0.78	0.3	0.226	1.025	
5:00	7½									

Nov. 1, 1916, she was tested with 30 gm. of glucose. The results are shown in Chart 16 and Table 9. The interesting points are the high preformed sugar value, the rapid and high hyperglycemia, the delay in returning to normal, and the permeability point to glucose being but slightly above the preformed sugar value, explaining the rapid appearance of glycosuria.

Alimentary Glucose Test in a Case of Hyperthyroidism

CASE 8.—J. K., male, aged 42, for the previous four months had weakness, loss of weight, irritability, tremors, palpitation, tachycardia, exophthalmos, enlarged pulsating thyroid, and glycosuria following meals. On the morning of May 20, 1915, he was given a hypodermic injection of 0.66 mg. of epinephrin. The results are shown in Chart 17 and Table 10. The preformed sugar was at the highest normal limit, probably due to his anxiety over the test. The kidneys actively excreted sugar when the blood sugar was between 0.165 and 0.171 per cent. Blood volume increased 3 per cent. during the development of the hyperglycemia (as shown by hemoglobin).

May 26, 1915, he was again tested with 1 mg. epinephrin hypodermically. The results are shown in Chart 18 and Table 11. Sugar appeared in the urine at a blood sugar concentration of 0.165 per cent. The hyperglycemia was more rapid, higher and more prolonged than when the smaller amount of epinephrin was given.

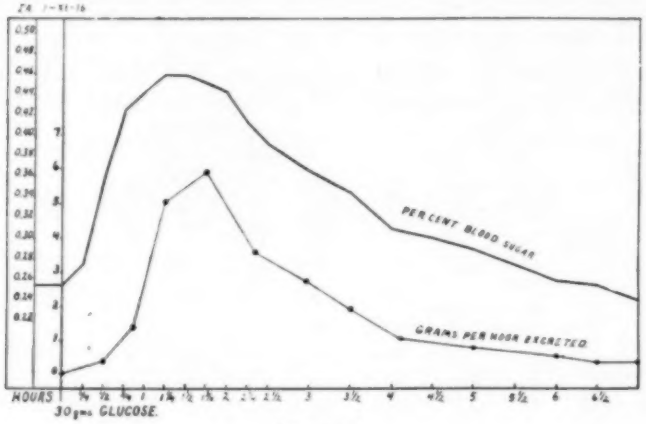

Chart 16

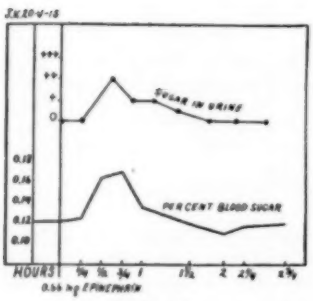

Chart 17

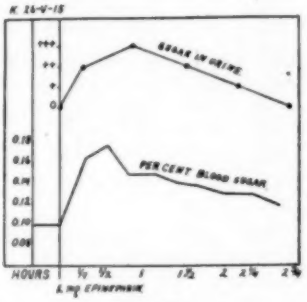

Chart 18

May 28, he was tested with 33 gm. of glucose. The results are shown in Chart 19 and Table 12. The blood sugar curve is of the normal type. Sugar was excreted at a blood sugar concentration between 0.15 and 0.174 per cent. Blood volume increased 5 per cent.

In these three tests the excretion of sugar closely followed the changes in blood sugar.

Alimentary Glucose Test in a Case of Myxedema

Case 9.—M., male, aged 54, for the previous four years had obesity, falling hair, lassitude, mental hebetude, myxedema of face, limbs, and abdomen, atrophy of thyroid gland and myocarditis. Blood pressure: systolic, 125; diastolic, 85. Phenolsulphonephthalein excreted in two hours time, 53 per

TABLE 10 (CASE 8, J. K., 5/20/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF HYPERTHYROIDISM

Time A. M.	Hr.	Blood Pressure	Blood: Hemoglobin Units	Blood: Sugar, per Cent.	Urine Sugar	Fluid Intake, C.c.
10:25	...	132-50	72	0.122	0.0	250
10:30	0.66 mg. epinephrin (hypo.)					
10:45	¼	160-70	69	0.124	0.0	
11:00	½	140-75	69	0.165	0.0	
11:15	¾	138-72	69	0.171	++	
11:30	1	133-60	69	0.136	+	
11:45	...	.....	..	.....	...	250
P. M.						
12:05	1½	125-63	69	0.12	0	
12:30	2	130-64	70	0.11	0.0	
12:45	2¼	132-65	70	0.118	0.0	
1:15	2¾	140-68	72	0.12	0.0	

TABLE 11 (CASE 8, J. K., 5/26/15).—SECOND TEST WITH EPINEPHRIN

Time P. M.	Hr.	Blood Pressure	Blood Sugar, per Cent.	Urine: C.c. per Hour	Urine: Sugar	Fluid Intake, C.c.
1:55	...	155-75	0.1	78.0	0.0	
2:05	1 mg. epinephrin (hypo.)					
2:25	¼+	193-70	0.165	18.0	++	250
2:40	½+	145-65	0.177			
2:55	1 —	132-60	0.147	36.0	+++	
3:05						
3:15	1¼—[5]	130-55	0.147			
3:30	1½—	125-55	0.141	49.0	++	
3:45	1¾—	126-60	0.134			
4:05	2	130-65	0.132			
				120.0	+	
4:25	2¼+	130-78	0.130			
4:45	2¾—	123-62	0.118	56.0	0.0	
5:00						

TABLE 12 (CASE 8, J. K., 5/28/15).—GLUCOSE TEST

Time A. M.	Hr.	Blood: Hemoglobin, Units	Blood: Sugar, per Cent.	Urine: C.c. per Hour	Urine: Sugar, Per Cent.	Urine: Sugar, Gm. per Hour	Fluid Intake, C.c.
10:05	...	75.5	0.116	?	0.0	0.0	
10:30	33 gm. glucose	.....	.....	..	...	...	300
				48	0.0	0.0	
10:45	¼	71.0	0.15				
11:00	½	70.5	0.174	78	0.27	0.05	
11:15	¾	68.0	0.188	62	1.0	0.6	
11:25							
11:30	1	69.5	0.192	60	0.9	0.54	
11:45							
12:00 M.	1½	70.5	0.18	63	0.5	0.3	
P. M.							
12:15	...	.....	.....	..	...	...	300
12:30	2	70.5	0.129	48	0.2	0.09	
12:45							
1:00	2½	71.5	0.104	78	0.0	0.0	
1:15							
1:30	3	72.0	0.118	62	0.0	0.0	
1:40							
2:00	3½	76.0	0.114	37	0.0	0.0	
2:15							
3:15	4¾	74.5	0.116	42	0.0	0.0	
3:45	5¼	75.0	0.112	36	0.0	0.0	

cent. Blood chemistry: urea nitrogen, 20 mg. per 100 c.c. blood; uric acid, 4.2 mg. per 100 c.c. blood; creatinin, 1.7 mg. per 100 c.c. blood.

July 9, 1915, he was tested with 1 mg. of epinephrin hypodermically. The results are shown in Chart 20 and Table 13. The preformed blood sugar was of normal value. The increase in blood sugar was very slow, the highest point being reached in from one to one and one-quarter hours, and had not returned to normal at the end of three and one-half hours. The highest blood sugar value was 0.141 per cent. and at no time was sugar excreted.

July 15, he was tested with 90 gm. of glucose. The results are shown in Chart 21 and Table 14. The preformed blood sugar was within normal limits. The blood sugar curve reached its highest point in one hour, but did not return to normal before the three and one-half to four-hour period. At no

TABLE 13 (CASE 9, M., 7/9/15).—ALIMENTARY GLUCOSE TEST IN A CASE OF MYXEDEMA

Time A. M.	Hr.	Hemoglobin Units	Blood Sugar, per Cent.	Urine Sugar
9:25	...	69	0.112	0.0
9:30	1 mg. epinephrin (hypo.)			
9:45	¼	65	0.12	0.0
10:00	½	70	0.132	0.0
10:15	¾	68	0.138	
10:30	1	67	0.141	0.0
10:45	1¼	70	0.141	
11:00	1½	68	0.138	
11:15	1¾	68	0.138	
11:30	2	68	0.135	0.0
11:45	2¼	64	0.132	
12:00 M.	2½	66	0.129	
P. M.				
12:15	2¾	63	0.126	
12:30	3	65	0.126	0.0
12:45	3¼	66	0.126	
1:00	3½	66	0.126	

TABLE 14 (CASE 9, M., 7/15/15).—GLUCOSE TEST

Time A. M.	Hr.	Hemoglobin Units	Blood Sugar, per Cent.	Urine Sugar, per Cent.	Fluid Intake, C.c.
9:00	...	68.0	0.12	0.0	
9:15	90 gm. glucose	....	.....	...	400
9:45	½	64.0	0.188	0.0	
10:00	¾	66.0	0.212		
10:15	1	67.0	0.216	0.0	
10:30	1¼	68.0	0.204		
10:45	1½	68.0	0.2		
11:00	1¾	68.0	0.196	0.0	
11:15	2	67.0	0.188		
11:45	2½	68.0	0.18		
P. M.					
12:15	3	68.0	0.156	0.0	
12:45	3½	68.0	0.135		
1:15	4	67.0	0.094		
1:45	4½	68.0	0.096	0.0	
2:15	5	67.5	0.104		
2:55	5¾	68.0	0.106		
3:30	6¼	68.0	0.112	0.0	

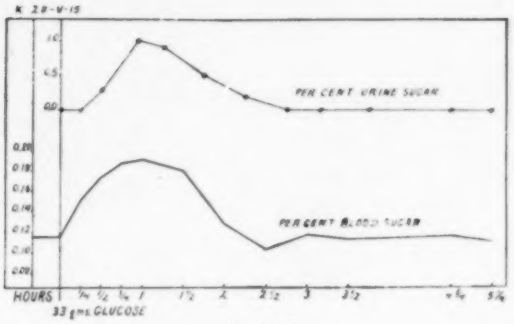

Chart 19

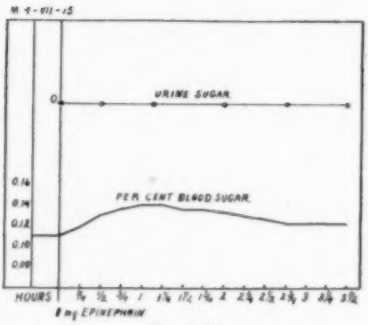

Chart 20

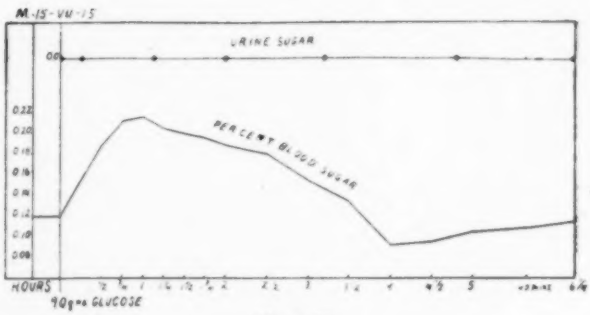

Chart 21

time was sugar excreted, although the blood sugar had reached a concentration of 0.216 per cent. Blood volume increased 4 per cent. on the development of the hyperglycemia, returning to normal as the blood sugar decreased.

The observations of Janney and Isaacson[26] on the blood sugar in thyroid and other endocrine diseases are of interest in connection with this and the following case.

Alimentary Glucose Test in Hypopituitarism

CASE 10.—E. L., female, aged 18, had the hypophysis removed by operation one year prior to admission. Marked obesity. Urine volume, 6,000 c.c. daily. No sugar, protein, or casts. Phenolsulphonephthalein, 62 per cent. excreted in two hours. Blood chemistry: urea nitrogen, 10 mg. per 100 c.c. blood; uric acid, 3.1 mg. per 100 c.c. blood; creatinin 1.8 mg. per 100 c.c. blood. The patient had been tested on two occasions with 250 gm. of glucose, and the twenty-four-hour specimen examined for sugar without any being found.

TABLE 15 (CASE 10, E. L., 1/31/16).—ALIMENTARY GLUCOSE TEST IN HYPOPITUITARISM

Time		Blood			Urine					Fluid Intake, C.c.
			Sugar				Sugar		Chlorids, Gm. per Hour	
A. M.	Hr.	Hemoglobin, Units	In Whole Blood, per Cent.	In Plasma, per Cent.	C.c. per Hour	Sp. Gr.	Per Cent.	Gm. per Hour		
9:35	...	71	0.12	0.105	270.0	1.010	0.0	0.0	0.216	
10:15	240 gm. glucose		.....	.....	.....	.....	...	....	....	400
10:30	¼	71	0.259	0.224	36.0	1.014	0.2	0.72	0.1	
10:45	½	68	0.315	0.297						
11:00	vomited 36.9 gm. glucose									
10:10										
11:15	1	67	0.369	0.351	288.0	1.024	0.9	2.59	0.4	
11:45	1½	66	0.378	0.333						
12:00 M.										
P. M.										
12:15	2	67	0.344	0.304	342.0	1.023	0.4	1.36	0.27	
1:00	2¾	67	0.287	0.252						
1:15	...	..	.....	.....	.....	.....	...	....	....	240
1:30	3¼	68	0.252	0.222	192.0	1.009	0.0	0.0	0.192	
2:30	4¼	68	0.184	0.16						
2:40	...	..	.....	.....	.....	.....	...	....	....	240
3:45	5½	68	0.105	0.066	306.0	1.022	0.0	0.0	0.24	
4:00										

Jan. 31, 1916, she was tested with 240 gm. of glucose. This was dissolved in 400 c.c. of weak tea and administered by means of a small stomach tube. The results are shown in Chart 22 and Table 15. The preformed blood sugar was within normal limits. Alimentary hyperglycemia reached its highest point in one and one-half hours, and returned to normal in five and one-half hours. Notwithstanding the high concentration of blood sugar, 0.378 per cent., the excretion of glucose was comparatively slight. Sugar was actively excreted at a blood sugar concentration of 0.26 per cent.

26. Janney and Isaacson: Arch. Int. Med. **22**:160, 1918.

The excretion of urine greatly decreased in the three-quarters hour following the ingestion of the glucose, later increasing. The excretion of chlorids decreased as the glucose solution was being absorbed.

Blood volume increased 5 per cent. (as indicated by hemoglobin decrease) during the hyperglycemia, later returning to normal.

Alimentary Glucose Test in a Case of Dyspituitarism

CASE 11.—S., male, aged 27, was obese, of feminine figure, with small wrists, tapering fingers, beardless face, and was mentally inferior. His morning blood sugar was 0.1 per cent.

TABLE 16 (CASE 11, S., 5/12/16).—ALIMENTARY GLUCOSE TEST IN A CASE OF DYSPITUITARISM

Time		Blood				Urine			Fluid Intake, C.c.
			Sugar						
A. M.	Hr.	Hemoglobin, Units	In Whole Blood, per Cent.	In Plasma, per Cent.	In Corpuscles, per Cent.	C.c. per Hour	Sp. Gr.	Sugar	
9:25	...	75	0.132	0.10	0.123	30	1.025	0	400
9:30	75 gm. glucose		.....	.....	.....	..	.....	...	
						25	1.030	0	
9:45	¼	72	0.178	0.2	0.2				
10:00	½	70	0.198	0.197	0.188				
10:15	¾	69	0.193	0.18	0.172	21	1.033	0	
10:40	1¼	70	0.183	0.156	0.172				
11:00	1½	69	0.148	0.14	0.155	43	1.036	0	
11:30	2	71	0.132	0.111	0.134				
12:00 M.	2½	73	0.118	0.094	0.128	20	1.041	0	
P. M.									
12:30	3	74	0.097	0.086	0.114				
						21	1.040	0	
1:15	3¾	74	0.111	0.099	0.123				
						21	1.043	0	
2:00	4½	73	0.111	0.114	0.128				
2:30	5	74	0.112	0.105	0.141	16	1.043	0	
3:00	5½	76	0.118	0.111	0.141				
						15	1.040	0	
4:00	6½	75	0.108	0.111	0.141				

May 12, 1916, he was tested with 75 gm. of glucose. The results are shown in Chart 23 and Table 16. The preformed blood sugar was slightly above normal. The blood sugar curve was of normal type. The urine remained free from sugar, although the blood sugar had reached a concentration of 0.198 per cent. The excretion of urine decreased during the development of the hyperglycemia, increasing as the blood sugar began to fall.

Hemoglobin estimations showed a blood volume increase of 6 per cent., which returned to normal with the blood sugar.

Alimentary Glucose Test in a Case of Parenchymatous Nephritis with Constant Glycosuria

CASE 12.—J. P., male, aged 62, had symptoms of nephritis for the previous two years. No symptoms of diabetes mellitus. For the previous six months he had generalized edema, retinitis, cardiac hypertrophy. Blood pressure: systolic, 190; diastolic, 130. Urine, 625 c.c., specific gravity, 1.025; dry protein per liter, 3.1 gm.; chlorids, 6.6 gm.; sugar, 0.6 per cent.; many hyaline and granular casts. Phenolsulphonephthalein excreted in two-hour test, 8 per cent. Blood chemistry: sugar, 0.18 per cent.; urea nitrogen, 23 mg.; uric acid, 4 mg.; creatinin, 1.9 mg. per 100 c.c. of blood. For ten months, up to the time of the patient's death, the urine constantly contained glucose, the concentration always being in the neighborhood of 0.5 per cent.

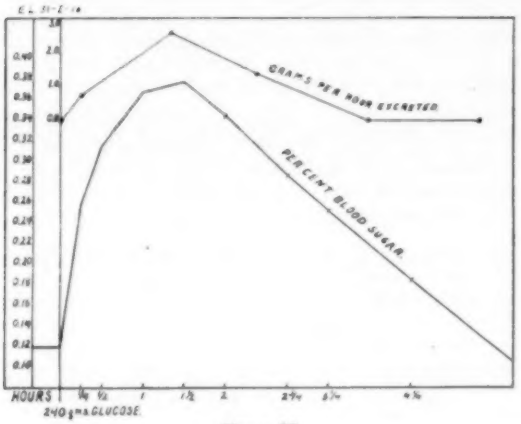

Chart 22

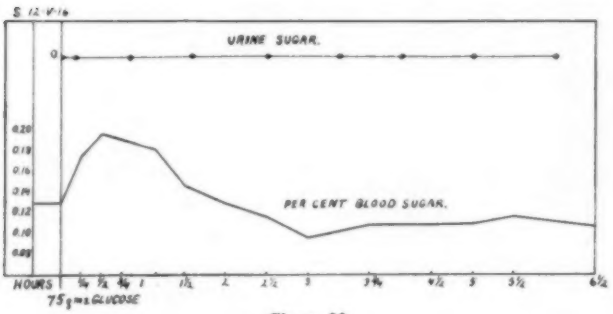

Chart 23

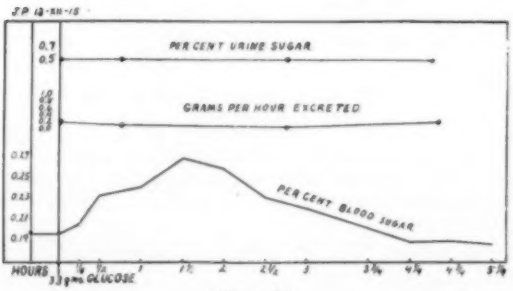

Chart 24

Dec. 13, 1915, the patient was tested with 33 gm. of glucose. The results are shown in Chart 24 and Table 17. The preformed blood sugar was high, as commonly found in nephritis. The blood sugar curve was greatly prolonged, the highest point being reached in one and one-half hours, not returning to normal before four and one-half hours had elapsed. The urine passed in this period contained about 0.5 per cent. glucose, and this independent of the blood sugar concentration. The actual excretion of glucose was less during the hyperglycemia than during the fasting state. In this case the sugar excretion varied directly with the excretion of urine.

March 11, 1916, the test was repeated, using 75 gm. of glucose. The results are shown in Chart 25 and Table 18. Again in this test the excretion of glucose was less during the hyperglycemia, although the urine sugar increased to 1.1 per cent. The time periods for the blood sugar curve are slightly longer than in the previous test; less than half the amount of glucose was ingested.

In each of these tests the excretion of urine decreased following the ingestion of glucose. Hemoglobin decreased during the development of the hyperglycemia, indicating an increase in blood volume at this time. The volume returned to normal on the subsidence of the hyperglycemia. Table 17 shows a decreased excretion of chlorids as the blood sugar increased. This retention is probably due to the increase in body fluid from the fluid intake and decreased excretion of urine.

TABLE 17 (CASE 12, J. P., 12/13/15).—GLUCOSE TEST IN PARENCHYMATOUS NEPHRITIS WITH CONSTANT GLYCOSURIA

Time		Blood		Urine					Fluid Intake, C.c.
		Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Sugar		Sp. Gr.	Chlorids, Gm. per Hour	
A. M.	Hr.				Per Cent.	Gm. per Hour			
9:25	...	67.5	0.196	42	0.52	0.22	1.015	0.193	
9:30	33 gm. glucose		.....	..	....	....	.....	.....	250
9:45	¼	64.0	0.208						
10:00	½	65.0	0.234	..	....	....	.....	.....	250
				36	0.51	0.180	1.015	0.123	
10:30	1	65.5	0.24						
11:00	1½	67.5	0.27						
11:30	2	67.0	0.26						
12:00 M.	2½	68.0	0.232						
P. M.									
12:30	3	67.5	0.224	33	0.51	0.17	1.016	0.142	
1:15	3¾	67.5	0.204						
1:30									
1:45	4¼	67.5	0.196						
2:15	4¾	68.0	0.196	42	0.52	0.21	1.013	0.19	
2:45	5¼	67.5	0.192						

SUMMARY

In the series of cases reported one finds variations in the blood sugar value after fifteen hours' fasting. Normal values are found in cases of renal diabetes, early mild diabetes, hyperthyroidism, hypothyroidism, hypopituitarism, dyspituitarism, and in a normal case. High blood sugar values are found in cases of nephritis, and diabetes of long standing with or without renal involvement. In the synchronous urine specimens two only showed the presence of glucose by Benedict's test. One was from a patient with a blood sugar of 0.098 per cent. whose kidneys at that time were excreting glucose at the rate of 2 gm. per hour. The other case showed a constant glycosuria of 0.5 per cent. independent of the diet.

In the twenty-four-hour urine specimens, glucose was found in the cases of renal diabetes, early mild diabetes, diabetes with and without renal involvement, hyperthyroidism, and chronic parenchymatous nephritis with constant glycosuria.

TABLE 18 (Case 12, J. P., 3/11/16).—Second Test

Time		Blood		Urine				Fluid Intake, C.c.
		Hemoglobin, Units	Sugar, per Cent.	C.c. per Hour	Sp. Gr.	Sugar		
A. M.	Hr.					Per Cent.	Gm. per Hour	
9:20	...	65.0	0.2	144	1.015	0.5	0.72	
9:30	75 gm. glucose		.....	...	.....	...	....	450
9.45	¼	65.0	0.258					
10:05	½	65.0	0.256					
10:20	¾	64.0	0.252	82	1.013	1.0	0.52	
10:35	1	64.0	0.329					
								250
11:00	1½	63.5	0.368					
11:20								
11:30	2	63.5	0.405					
								500
P. M.								
12:45	3¼	64.0	0.39	56	1.015	1.1	0.61	
1:30								
3:15	5¾	65.0	0.25					
4:15	6¾	65.0	0.22	?	1.014	0.5	?	
7:35								

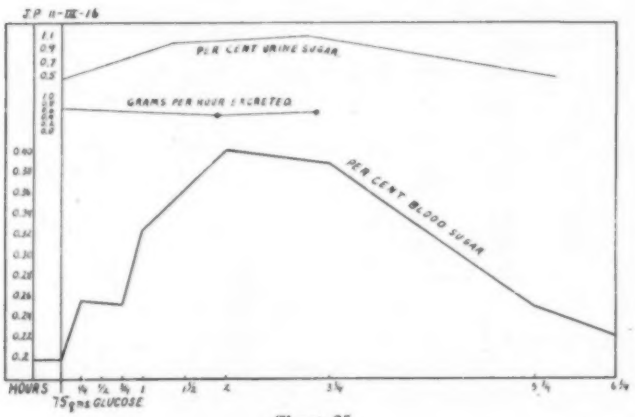

Chart 25

Following the ingestion of glucose the type of blood sugar curve varied in the different cases, showing a rapid increase and decrease in uncomplicated mild diabetes; in the cases of dyspituitarism, hyperthyroidism, renal diabetes, and normal, the curves are of the type found in normal individuals by various investigators.

In nephritis the curve was delayed and prolonged. In diabetes with renal involvement, the increase in blood sugar was at the normal rate, but there was a very slow return to the preformed value.

A higher blood sugar at the end of the first hour than at the end of the second was found in normal, renal diabetes, early mild diabetes, diabetes of long standing without renal involvement, diabetes with cardiac incompetence, hyperthyroidism, myxedema, hypopituitarism, and dyspituitarism.

Higher values at the end of the second hour were found in chronic interstitial nephritis, diabetes with interstitial nephritis, and chronic parenchymatous nephritis with constant glycosuria.

The concentration of blood sugar at which glycuresis occurred varied greatly in these cases, being less than 0.088 per cent. in the case of renal diabetes, 0.125 per cent. in early mild diabetes, 0.165 per cent. in hyperthyroidism, 0.167 per cent. in the normal case, 0.2+ per cent. in dyspituitarism, 0.216 per cent. in hypothyroidism, 0.26+ per cent. in hypopituitarism, 0.29 per cent. in nephritis, and 0.3+ per cent. in two cases of diabetes with renal involvement.

Cases showing an excretion of over 1 gm. of sugar in the six hours following the ingestion of from 60 to 75 gm. of glucose were: renal diabetes, early mild diabetes, diabetes of long standing without renal involvement, parenchymatous nephritis with constant glycosuria, those excreting less than 1 gm. were normal, interstitial nephritis, myxedema and dyspituitarism.

Cases showing an excretion of more than 1 gm. in the six hours following the ingestion of 30 to 33 gm. of glucose were renal diabetes, diabetes with renal involvement, parenchymatous nephritis with constant glycosuria; those excreting less than 1 gm. were: early mild diabetes, diabetes with cardiac incompetence, and hyperthyroidism.

The rate of sugar excretion was uninfluenced by changes in excretion of urine in all excepting Case 12. In this patient glycosuria varied directly with the amount of urine excreted and not according to changes in the blood sugar. A similar case has been reported by Epstein[21] (Chart 26).

Sixty estimations are given comparing the sugar content of whole blood and that of plasma. The results show 15 per cent. more in whole blood than in plasma. (A source of error in the technic employed lies in the fact that the plasma specimens were allowed to stand at room temperature for half an hour, during which time glycolysis may have occurred; the whole blood estimates were made at once.)

In twenty-six estimations the corpuscles contained 5 per cent. more reducing substance than the plasma (the technic being the same for both).

In thirteen tests, changes in blood volume were recorded following the ingestion of glucose. During the rise in blood sugar, blood volume increased from 1 to 7.5 per cent. (the average increase being 4.2 per cent.). The volume returned to normal on the subsidence of the hyperglycemia.

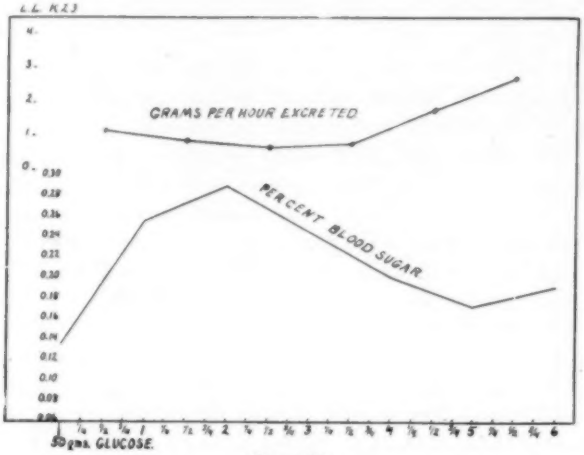

Chart 26

CONCLUSIONS

1. Sugar is a constant constituent of normal urine, and, during a fasting and thirsting state, the concentration in the urine approximates that in the blood.

2. Following the administration of small amounts of glucose (30 gm. or less) the blood sugar increases, and its demonstration depends entirely on the frequency of the estimations.

3. In a normal person the sugar in the urine parallels that in the blood up to the latter's concentration of 0.16 to 0.17 per cent. Above that the kidneys actively excrete sugar. In returning to the normal value the decrease in blood sugar precedes that in the urine.

4. Alimentary hyperglycemia in uncomplicated diabetes is characterized by a rapid rise and fall.

5. When diabetes is complicated by renal involvement, alimentary hyperglycemia is prolonged.

6. Alimentary hyperglycemia is prolonged in myxedema and hypopituitarism.

7. In nephritis alimentary hyperglycemia is delayed and prolonged.

8. The concentration of blood sugar at which glycuresis occurs varies in different individuals, and is influenced by disease, being abnormally low in early diabetes, high in diabetes of long standing; in nephritis, and in deficiency of the thyroid or hypophysis.

9. Glycuresis is a kidney function and is excessive in diabetes and hyperthyroidism. It is greatly decreased in nephritis and in deficiency of the thyroid or hypophysis.

10. Blood sugar estimations one hour after the ingestion of glucose may be the same in renal diabetes, early diabetes, or normal cases.

11. Blood sugar estimations two hours and three hours after the ingestion of glucose may be the same in diabetes of long standing, in nephritis, myxedema, or in hypopituitarism.

12. Blood volume increases with the development of a hyperglycemia, returning to normal with the blood sugar.

13. Blood sugar is about equally divided between plasma and corpuscles.

14. Sugar in the corpuscles increases in proportion to that in the plasma.

15. Excretion of sugar is uninfluenced by the rate of urinary excretion, excepting in some cases of parenchymatous nephritis.

16. Morning blood sugar estimations are of great diagnostic value. The urine excreted at the same time should be tested for sugar and the rate of excretion determined. As the morning blood sugar varies under treatment, diagnostic tests should be made after the patient has been on regular diet for several days.

17. Tests of alimentary hyperglycemia are of little clinical value; especially is this true of tests made at one hour intervals.

18. Examination of the twenty-four-hour urine for sugar (Benedict's new method[27]), or better, fractional examinations, detects cases of excessive glycuresis.

19. Test of alimentary glycuresis following the ingestion of glucose (100 gm. for a person of average weight, that is, 1.7 gm. per kilogram) is a valuable diagnostic and prognostic method, the urine sugar being estimated at frequent intervals for the succeeding six hours, and the total excretion determined. This, in conjunction with the morning blood and synchronous urine sugar estimation, probably tells us as much about the case as do the elaborate tests herein reported.

I wish to thank Prof. Edward Quintard, director of the Department of Medicine, and Prof. Victor C. Myers, director of the Laboratory of Pathological Chemistry, for their many courtesies, help and advice.

303 East Twentieth Street.

27. The conclusions regarding clinical tests are largely in accord with those of Rogers: Boston M. & S. J. **175**:152 (Aug. 3) 1916.

DIASTATIC ACTIVITY OF THE BLOOD IN CANCER, SYPHILIS AND DIABETES*

H. H. DeNIORD, M.D., AND B. F. SCHREINER, M.D.
BUFFALO

Some interesting observations were made by V. C. Meyers and J. A. Killian[1] on the diastatic activity of the blood, and we have for some months past included an estimation of the diastatic activities of the blood in our routine complete blood studies. We have followed the method of Lewis and Benedict for blood sugar estimation and that of Meyers and Killian for the diastatic activity in the blood, being exact in the period of incubation, and beginning the blood chemistry work within ten minutes after the withdrawal of blood from the vein.

In the routine studies of the blood of cancer patients of the State Institute for the Study of Malignant Disease we have accumulated considerable data on other estimable blood factors, but in this short paper we are reporting only on the Wassermann reaction, diastatic activity and sugar content of the blood, and the effect of roentgen-ray treatments on these factors. We have also included in our report similar studies of diabetics and nephritics, eclamptics, cases of general fatigue and overwork, and normal people. The most interesting of our observations have been those made in our studies of the cases of diabetes, in the behavior of the diastatic activity of the blood. After an observation of a large series of cases we have taken this factor to be normal up to an activity of 40.

DIASTATIC ACTIVITY OF THE BLOOD IN GLYCOSURIA

Glycosuria may be divided into four groups:

(*a*). La piqure of Claude Bernard.

(*b*). Alimentary glycosuria.

(*c*). Phloridzin diabetes.

(*d*). Pancreatic diabetes.

(*a*). Claude Bernard, the originator of la piqure, has shown unquestionably the relation of injury of a group of medulla cells to glycosuria. This type is unobtainable in a starving animal and is entirely dependent on glycogenolysis. It has been attributed to sudden flushing of the liver with blood, causing a rapid conversion of glycogen

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*From the New York State Institute for the Study of Malignant Disease, Buffalo, N. Y., H. R. Gaylord, M.D., Director.

1. Meyers and Killian: Jour. Biol. Chem. **29**:179, 1917.

to sugar. It may be due to a sudden activation of diastase in the blood, from some source or other, stimulated by the injury to the nerve tissue; or to a lowering of the threshold of excretion of sugar in the kidneys.

Much remains to be said about hyperglycemia in this type of glycosuria.

(*b*) Alimentary glycosuria is frequent in its occurrence, appears with an intestinal stasis and toxemia with poor oxidation, and disappears on correction of these ailments. It may exist with quite normal kidneys with a glycemia of but 150 to 200 mg. of dextrose per 100 c.c. of blood, and in nephritis the dextrose may arrive at a concentration of 200 to 400 mg. before it begins to be excreted, depending on the severity of the renal lesion. It is possible that putrefaction products in constipation cause an inhibition of glycogenesis or a much inhibited sugar utilization. Further investigation of ferment activity is needed to throw light on this subject.

(*c*) Phloridzin diabetes, purely an experimental type, suggests only the changes possible in the permeability of renal cells to different blood factors, and adds strength to the much discussed question of selective retention of the various products normally excreted by the kidneys from the blood.

Loewi[2] believes that it converts colloidal blood sugar into diffusible blood sugar, resulting in an immediate diffusion through the renal cells, which are unaffected by the phloridzin. Stiles and Lusk[3] have shown that dextrose, uniting with the colloidal radical in the blood, is not burned, and that dextrose injected subcutaneously reappears in the urine. On the other hand, Rosenfeld and Asher[4] find blood sugar readily diffusible. Therefore, the action of phloridzin must be in increasing the permeability of the renal cell membranes, rather than in altering the chemical state of the sugar.

To digress somewhat on the subject of phloridzin glycosuria, consider for a minute the question of permeability of membranes and the important bearing it must have on carbohydrate metabolism. The carbohydrates of the food are absorbed into the portal circulation as a monosaccharid, and some of this is stored as the polysaccharid, glycogen, in the liver. A portion not stored here is deposited in the muscles also as glycogen; a part of it is utilized immediately by the tissues for work and heat; some glucose remains in the blood stream for the maintenance of the normal concentration of sugar in the blood. Normally, on absorption of sugar there is an immediate stimulus to storage of this material in the tissue cells. The so-called "stimulus" must be merely a mechanical factor of the fluid on the outside of the

2. Loewi: Arch. f. exper. Path. u. Pharmakol. **48**:410, 1902.
3. Stiles and Lusk: Science of Nutrition, p. 274.
4. Rosenfeld and Asher: Zentralbl. f. Physiol. **14**:449, 1905.

cell membranes becoming hyper-isotonic to the fluid inside, and the membrane being wholly permeable to sugar admits it until the fluids are again isotonic, or in balance. This process is shortened by the burning of some of the sugar, and the time covered by the entire procedure is two to three hours, when the normal level of the blood sugar is reached. At the moment this occurs, a reverse process begins. The blood sugar continues to be burned, which makes the blood hypo-isotonic to the cell fluid and osmosis reverses, with active glycogenolysis, until food ingestion adds a fresh supply of sugar to the blood. There is then a constant flow of sugar molecules either into or out of the cell, with possibly other substances permeable through this membrane.

With a persistent hyperglycemia and no glycogen storage, there undoubtedly is some change in the cell membrane which converts it to a membrane semipermeable to sugar and prevents its storage.

In phloridzin diabetes the renal cell membrane must undergo some change which, on the other hand, converts it from a semipermeable to a perfectly permeable membrane.

In alimentary glycosuria the hyper-isotonic state of the sugar of the blood to that of the tissue cells raises considerable osmotic pressure, which may stimulate the renal cells so that sugar is excreted. The point of osmotic tension at which glycosuria commences varies with the individual, and depends considerably on the state of the kidney and whether it is normal; so that in varying degrees of nephritis, the osmotic pressure of the sugar in the blood must rise higher in order to have a glycosuria. The patient begins to excrete sugar as soon as the threshold of excretion of that material is reached. He also responds with exactness to restriction of carbohydrates in his diet until the sugar in his blood becomes normal, when there is once more a normal balance in glycolysis and glycogenolysis and a distinct relief of the irritating high osmotic pressure on the renal cells. This relieves the irritating symptoms of polyuria so common to glycosuria, and especially in chronic interstitial nephritis.

The question resolves itself into what can change the permeability of a membrane? The agent in the blood that does this cannot be incorporated in fixed tissue cells, but must be an internal secretion carried by the blood. All tissues contain diastase, but not all of them contain activators of this ferment. The one tissue which we know contains both is the blood.

(*d*). Pancreatic diabetes has long been a subject of research, and we are little farther advanced than Claude Bernard left us in 1856. Von Mering and Minkowski,[5] in 1892, proved that the depancreatinized

5. Von Mering and Minkowski: Arch. f. exper. Path. u. Pharmakol. **26**:371, 1890.

dog has an extreme diabetes; while if a piece of pancreas be ingrafted under the skin of the dog, he remains sugar-free for two months, but on extirpation of the graft, diabetes is precipitated and the dog dies.

It has been generally conceded that the pancreas has an internal secretion that controls carbohydrate metabolism; and Baumel, Lemain and Lannois, Lepine and Audry with several other observers are satisfied that the Islands of Langerhans in the pancreas are the secreting cells of its internal secretion.

DeMeyer[6] shows that the liver from a depancreatized animal, perfused with Ringer's solution can have storage of glycogen function restored by adding pancreatic extract. He does not say whether the addition of any other glandular extract will be similarly effective. Von Mering and Minkowski have shown that diabetes is not a nerve lesion; nor an alteration of liver function through impaired circulation; nor an impairment of digestion of carbohydrates.

Harley[7] assures us that the glycosuria is not due to injury of the nerves of the celiac plexus, but solely to "total arrest of pancreatic function," and adds that the entire pancreas, rather than the islands alone, plays the part.

Pathologists agree on the findings in diabetes.

Cecil,[8] in 1908, reported very completely ninety cases of diabetes with pathologic-anatomic studies, and found that 79 per cent. of these cases had definite anatomic changes in the islands. Of these, 40 per cent. had a moderate sclerosis and 35 per cent. advanced sclerosis. Lydia DeWitt,[9] in a large series of cases, observed that the Islands of Langerhans contain more connective tissue with advancing age — but this is characteristic of all parenchyma.

Cecil[8] mentions one case in particular with marked pancreatic lipomatosis coming to necropsy. There had been no diabetes, yet only a small fraction of the parenchyma survived; which, however, compensated for the lost tissue in being very rich in well preserved Islands of Langerhans.

The islands in diabetes are found to be surrounded by thick fibrous sheaths. The fibrillary coating of insular capillaries is definitely increased in thickness, converting vessels to coarse septa which extend in from the capsule and anastomose at the center of the interacinar island. The cells forming the column show little change.

Considerable study has been made of other internal secreting organs with a view of finding a possible different source of material

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6. DeMeyer: Arch. de physiol. 1909-1910, pp. 1-100.
7. Harley: Jour. Anat. and Physiol., London **26**:204, 1891-1892.
8. Cecil (two papers): Med. and Surg. Rep. Presb. Hosp., New York **8**:173 and 217, 1908.
9. DeWitt: J. Exper. Med. **8**:193, 1906.

controlling carbohydrate metabolism. Cecil[9] thought of this and mentions several cases of changes in the pituitary gland besides sclerosis of the Islands of Langerhans in diabetes. With stimulation of adrenals by way of the sympathetic nerves, MacKenzie[10] found that glycogenolysis increased, and there was a hyperglycemia. It does not, however, cause a loss of glycolytic activity which is part of the altered metabolism in pancreatic diabetes. On extirpation of the adrenals in depancreatized dogs, the hyperglycemia disappears. There is no definite relation between the adrenal medulla and the Islands of Langerhans.

It is accepted that insufficient activity of the Islands of Langerhans will cause diabetes, but there are several other factors that may cause it, about which we as yet know nothing.

There are no records of the frequency of cirrhosis of the pancreas in syphilitics, but judging from the rapidity with which cirrhosis of all parenchyma occurs in this disease, it is not difficult to assume that the pancreas likewise suffers.

Warthin and Wilson,[11] Laignel[12] and Antoine[13] reported a relative frequency of the presence of syphilis in diabetics, but nothing has been said of the alteration of the blood chemistry in this type of case. The syphilitic diabetic is either diabetic because of his syphilis, or made much worse by it, and unquestionably the syphilitic diabetic has a much greater involvement of the Islands of Langerhans than the nonsyphilitic diabetic.

The diastatic activity of the blood of the ordinary syphilitic varies as normally; in the simple diabetic the diastatic activity is extremely high, ranging from 40 to 100, usually around 60 or 80, as Meyer and Killian[1] also noted. But without exception those diabetics who are syphilitic have a low diastatic activity, while both types have varying degrees of hyperglycemia.

Each of the five syphilitic diabetics in our records had a notably low carbohydrate tolerance, and we have thus far been unable to get a syphilitic diabetic under sufficiently long observation to state whether his increased tolerance rises to normal after the syphilis is cured, or whether some permanent ferment injury has been done. In one case, however, the patient came into the hospital with diabetes and gangrenous foot, improved rapidly in health and the foot healed after two arsphenamin treatments, and his carbohydrate tolerance almost doubled.

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10. MacKenzie, G. M.: Arch. Int. Med. **19**:593, 1917.
11. Warthin and Wilson: Am. J. Med. Sc. **152**:157, 1916.
12. Laignel: Rev. neurol., Paris **22**:481, 1914.
13. Antoine: Arch. méd. d'angus **17**:147, 1913.

The syphilitic diabetic has the most extreme loss of carbohydrate tolerance, which, it is our personal belief, will be checked on cure of the syphilis, if the patient is given the same dietetic care that any diabetic should receive, keeping the hyperglycemia reduced to normal.

If it is possible to have a low diastatic activity and diabetes, then the disease does not depend solely on glycogenolysis, but may be due to the failure of the tissues to hold or to burn sugar.

It seems incredible that the Islands of Langerhans should secrete an activating agent for diastase that sometimes activates and sometimes inhibits; but this must be true if we accept the idea that pancreatic diabetes and syphilitic diabetes have the same cause — insufficiency of the secretion of the Islands of Langerhans — for in one case the diastatic activity is very high and in the other low. The only explanation we can offer for this is that the Islands of Langerhans secrete a substance inhibitory to the action of diastase, and thereby control its activity. If this is true, then the increased diastatic activity in pancreatic diabetes is due to destruction of the islands so great that there is no inhibiting agent of diastase secreted, and the diastase in the blood is superactive.

In the syphilitic diabetic, cirrhosis is not confined to the islands of the pancreas, but involves all parenchymatous tissue. This encroaches on the secreting cells which, in turn, are irritated and stimulated to excessive secretion. The diastase is inhibited to a greater degree, with resultant low diastatic activity. One never finds increased diastatic activity with a hypo- or normal glycemia, but it is not uncommon to find hyperglycemia and a low diastatic activity. So we conclude that the hyperglycemia of diabetes is due to another cause than increase of glycogenolysis alone, and it probably is something affecting the permeability of cell membranes to sugar and inhibition of glycogenesis, so that all the sugar remains in the blood, to be excreted, or a very small portion burned.

Table 1 gives data of seventeen cases, of which six patients are syphilitic. Of these six, only one was suspected of having syphilis; the other five were well symptomatically, with the exception of their diabetes. Each case of simple diabetes shows the greatly increased diastatic function and hyperglycemia, and the syphilitic diabetics are characterized especially by their hyperglycemia and low or normal diastatic function. Several of the nonsyphilitic diabetics are somewhat atypical, with high sugars and not excessively actice diastatic functions.

Case 2, for instance, was a business man, exhausted by the long strain of an exacting business. With a complete rest and tolerance dieting, he made a complete recovery and now has a normal blood chemistry and tolerance for carbohydrates.

Case 4, a woman with a history of diabetes and deafness for four years, had a tolerance of 30 gm. of carbohydrates at the time the blood was taken, and was very weak. Improvement was striking with antisyphilitic treatment.

Case 1 was a ward patient brought in for gangrenous foot. He was given arsphenamin, and the foot healed uneventfully. The carbohydrate tolerance in this case increased from 35 gm. to 60 after the arsphenamin.

TABLE 1.—DIABETICS

Case	Sex	Age	Diagnosis	Wassermann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
1	♂	60	Diabetes	+++	400	20*
2	♂	48	Diabetes One month of rest and diet	Neg. Neg.	298 150	38 38
3	♂	28	Diabetes	+++	200	10*
4	♀	36	Diabetes	+++	400	25*
5	♀	65	Diabetes	Neg.	334	66
6	♂	60	Diabetes	Neg.	349	69
7	♀	60	Diabetes	+++	400	20*
8	♂	46	Diabetes	Neg.	405	75
9	♂	40	Diabetes	Neg.	435	113
10	♀	40	Diabetes	Neg.	400	102
11	♀	45	Diabetes and nephritis	+++	421	5*
12	♂	40	Diabetes	Neg.	400	44
13	♂	50	Diabetes	Neg.	266	46
14	♂	51	Diabetes	++	191	25*
15	♀	55	Diabetes	Neg.	261	62
16	♂	60	Diabetes (cancer) Half hour later Day later	Neg. Neg. Neg.	266 266 500	79 60 60
17	♂	61	Diabetes	Neg.	235	33

* Syphilitic.

Case 16 was a cancer patient with diabetes. His blood chemistry study was made before roentgen-ray treatment, one half hour after, and twenty-four hours after. The great increase in blood sugar on the day following the roentgen-ray treatment was due not to the roentgen ray, but to an excessive carbohydrate ingestion.

Case 17 is similar to Case 2. In this instance the patient had what his doctor called an alimentary glycosuria. His blood sugar increases only during periods of fatigue and his diastatic function remains normal.

Case 9 had been kept well below his tolerance of 75 gm. of carbohydrate, no glycosuria and with normal blood sugar for two years.

TABLE 2.—Tumor Cases with Roentgen-Ray Treatment

Case	Sex	Age	Diagnosis	Wassermann Reaction	Sugar, Mg. per 100 C.c.			Diastatic Activity		
					Before x-ray	Half Hour after x-ray	Day after x-ray	Before x-ray	Half Hour after x-ray	Day after x-ray
1	♂	50	Postoperative epithelioma of penis for 6 months; living	Neg.	142	190	235	11	42	34
2	♀	60	Epithelioma little finger, 13 years; improved	Neg.	222	210	181	28	30	22
3	♂	..	Epithelioma of face	Neg.	256	178	111	29	14	11
4	♂	31	Four months abdominal tumor; living	Neg.	222	200	68	28	17	17
5	♂	24	Sarcoma foot	Neg.	174	222	200	65	12	10
6	♀	65	Two years carcinoma left breast; living	Neg.	261	250	217	28	17	26
7	♂	31	Ten months adenocarcinoma cecum; well	Neg.	333	337	166	47	13	33
8	♂	35	Angioma lower lip, cured	Neg.	266	250	142	47	22	15
9	♂	52	Three months epithelioma left face	Neg.	182	182	175	20	30	28
10	♂	51	Sarcoma left neck, 1 year; living	Neg.	190	200	153	34	32	58
11	♀	57	Carcinoma left breast, 1 year; died	Neg.	133	142	200	11	12	10
12	♂	65	Epithelioma left face, 30 years; living	Neg.	160	114	153	8	8	28
13	♂	37	Melano sarcoma left groin, 1 year; died	Neg.	135	427	137	38	96	12
14	♀	54	Epithelioma of vulva; living	Neg.	133	100	118	38	50	21
15	♀	52	Epithelioma of vulva, 2 years; unimproved	Neg.	133	160	143	20	34	18
16	♀	51	Carcinoma right breast, 18 months; improved	Neg.	154	143	133	13	21	23
17	♀	52	Carcinoma left breast, 20 years; living	Neg.	182	121	100	13	11	37
18	♂	71	Carcinoma bladder	Neg.	143	121	133	10	6	25
19	♂	50	Lymphosarcoma of right tonsil, 1 year	Neg.	108	154	127	46	49	54
20	♂	57	Epithelioma left ear, 5 years; unimproved	Neg.	142	153	200	51	48	17
21	♀	66	Epithelioma nose, 2 yrs.; clinically well	Neg.	123	190	178	28	62	14
22	♂	46	Epithelioma lower lip, 1 year	Neg.	145	143	143	21	3	9
23	♂	82	Epithelioma of nose, 10 months; unimproved	Neg.	160	166	133	48	50	40
24	♂	64	Epithelioma right eye, 52 years; unimproved	Neg.	188	181	152	31	43	36
25	♀	44	Carcinoma of cervix, postoperative, 5 months; living	+++	164	181	166	44	47	44
26	♀	60	Carcinoma of right breast, operation, recurrent, 4 years; died	Neg.	174	143	87	44	18	47
27	♀	52	Carcinoma of uterus, 1 year; Died	Neg.	166	166	153	47	33	69
28	♂	46	Leukoplakia on mouth, 1 year; living	Neg.	68	82	...	68	66	
29	♀	54	Uterine infected fibroid, 2 years; living	Neg.	78	91	...	18	12	

He had been able to do hard work in a steel mill during this time, and an attack of influenza temporarily broke his tolerance, when the blood study was made. It is steadily improving now, however, and the carbohydrate tolerance is picking up.

We studied twenty-nine cases of malignancy and the effect of roentgen ray on their blood chemistry (Table 2). We are utilizing the data of the sugar and diastatic function here, and the other studies are to be reported later.

The cancer patient shows no special feature of carbohydrate metabolism. There is a tendency to hyperglycemia, but in every instance this is due to the high carbohydrate diet these people had been getting, together with lack of exercise. The bed patient invariably shows deficient oxidative powers. The cancer patients studied were being treated with the roentgen ray, and the blood was obtained before exposure, one-half hour after and twenty-four hours after. Of the cases studied, several patients had slight renal lesions; but the majority were normal as to blood chemistry: 7 cases had hyperglycemia; 21 had normal sugar before roentgen ray; 13 had sugar increased one-half hour after; 15 had decreased one-half hour after; 9 had increased the day after; 19 had decreased the day after.

Those cases in which the sugars were lowest following roentgen ray treatment had received the largest doses, so we can say that the roentgen ray certainly increases oxidation of blood sugar, but this is true of any individual whether he has a malignant disease or not. In half of the cases the diastatic activity had increased one-half hour after roentgen-ray treatment, and in the rest there was a decrease. On the day following roentgen-ray exposure the diastatic activity of half of the cases studied had increased, and in the rest it had decreased. As the diastatic activity of patients treated with the roentgen ray under similar conditions did not show a consistent increase or decrease either one-half hour after or the day after roentgen-ray treatment, we can say that the rays have no special or permanent effect on the diastatic activity of the blood.

In the fifty-two miscellaneous malignant cases recorded in Table 3 the blood sugar varies with the diet and exercise of the patient. The diastatic function has no special relation to any condition that could be considered specific or diagnostic for malignancy.

Those syphilitics with the additional disease of cancer do not necessarily have a low diastatic activity. On the other hand, many of the nonsyphilitic cases have extremely low diastatic activities.

Sixty-one miscellaneous cases (Table 4) show very much the same thing in their blood chemistry as regards the sugar and diastatic activity that the cancer cases show.

TABLE 3.—CANCER CASES NOT ROENTGEN-RAYED

Case	Sex	Age	Diagnosis	Wassermann Reaction	Blood Sugar, Mg. per 100 C.c.	Diastatic Function	Duration	Present Condition
1	♀	48	Myoma	++	166	17	1 yr.	Died
2	♂	70	Epithelioma of face	Neg.	166	18	1 yr.	Died
3	♀	60	Carcinoma right breast	Neg.	250	30	5 yr.	Died
4	♂	27	Syphilis; granuloma	+++	200	30	14 mo.	Clinicaly well
5	♂	50	Epithelioma right cheek	Neg.	188	38	2 yr.	Well
6	♀	36	Carcinoma uterus	+++	274	25	5 mo.	Died
7	♂	63	Papilloma bladder	Neg.	148	26	3 yr.	Unimproved
8	♀	39	Postoperative carcinoma cervix	Neg.	200	40	12 yr.	Unimproved
9	♀	65	Carcinoma breast	Neg.	118	23	2 yr.	Died
10	♀	61	Epithelioma nose	Neg.	160	26	1 yr.	Well
11	♀	61	Postoperative, recurrent carcinoma left breast	Neg.	117	7	7 mo.	Died
12	♂	41	Epithelioma lower gum	Neg.	153	22	6 mo.	Unimproved
13	♂	41	Epithelioma lip, lower	Neg.	130	40	4 yr.	Unimproved
14	♂	57	Epithelioma ear, left	Neg.	133	28	5 yr.	Living
15	♀	53	Carcinoma (colloid) rectum	Neg.	158	26	1 yr.	Living
16	♂	18	Epithelioma right upper jaw	Neg.	129	16	6 mo.	Died
17	♀	52	Carcinoma uterus	Neg.	153	19	1 yr.	Died
18	♀	49	Carcinoma uterus	Neg. (8/14/18)	123	25	9 wk.	Living
19	♀	49	.....	(8/24/18)	136	14		
20	♀	49	.....	(7/12/18)	117	31		
21	♀	62	Epithelioma shoulder, left	Neg.	235	47	30 yr.	Unimproved
22	♀	55	Melanosarcoma Archilles tendon	+?	160	48	46 yr.	Operated; well
23	♀	65	Carcinoma esophagus	Neg.	181	44	1 yr.	Living
24	♂	49	Syphilis and epithelioma soft palate	+++ (10/ 4/18)	190	50	4-5 mo.	Died
25	♂	49	.....	(8/21/18)	118	40		
26	♀	51	Carcinoma cervix	Neg.	172	38	1 yr.	Died
27	♀	42	Round cell sarcoma	Neg.	166	66	1 yr.	Living
28	♂	80	Carcinoma bladder	Neg.	400	80	1 yr.	Living
29	♀	45	Carcinoma stomach	Neg.	286	76	4 mo.	Died
30	♀	60	Epithelioma tongue	Neg.	196	46	6 mo.	Untreated
31	♀	61	Pyloric ulcer, obstruction	Neg.	154	39	all life	Living
32	♂	53	Mediastinal tumor	Neg.	285	23	3 mo.	Unimproved
33	♂	39	Carcinoma of breast	Neg.	250	30	2 yr.	No recurrence
34	♀	60	Epithelioma finger, left hand	Neg.	202	15	13 yr.	Improved
35	♀	39	Carcinoma cervix	++	166	47	6 mo.	Clinically well
36	♀	45	Carcinoma cervix	+	187	30	4 yr.	Improved
37	♀	59	Lymphosarcoma, probable primary in tonsil	Neg.	178	25	18 mo.	Unimproved
38	♀	43	Adenocarcinoma uterus	Neg.	238	19	10 yr.	Living

TABLE 3.—Cancer Cases Not Roentgen-Rayed—(*Continued*)

Case	Sex	Age	Diagnosis	Wassermann Reaction	Blood Sugar, Mg. per 100 C.c.	Diastatic Function	Duration	Present Condition
39	♀	76	Epithelioma vulva	Neg.	149	44	8 mo.	Living
40	♀	51	Carcinoma ovary	Neg.	181	21	2 yr.	Living
41	♂	62	Gumma (bridge of nose)	Neg. (10/15/18)	166	24	1 yr.	Living
42	♂	..	.....	(10/22/18)	244	16		
43	♂	..	.....	(11/ 9/18)	181	64		
44	♂	74	Epithelioma epitrochlear region, prickle cell	+	244	31	5 mo.	Living
45	♀	29	Carcinoma uterus	Neg.	200	40	7 mo.	Unimproved
46	♀	52	Sarcoma of neck	++	181	36	4 mo.	Clinically well
47	♂	57	Epithelioma branchial remains	++	142	24	4 mo.	Unimproved
48	♀	34	Angioma eye	Neg.	166	15	32 yr.	Living
49	♀	66	Carcinoma uterus	Neg.	181	44	4 yr.	Improved
50	♀	31	Splenic anemia	Neg.	285	23	1 mo.	Unimproved
51	♀	65	Epithelioma of nose	Neg.	200	40	1 yr.	Well
52	♂	..	Epithelioma of scrotum	Neg.	250	50	5 yr.	Died

TABLE 4.—Miscellaneous Cases

Case	Sex	Age	Diagnosis	Wassermann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
1	♂	55	Nephritis	Neg.	298	40
2	♂	25	Nephritis	Neg.	105	41
3	♀	42	Nephritis	Neg.	181	97
4	♂	50	Nephritis	Neg.	202	39
5	♂	50	Nephritis	++	148	27
6	♂	45	Nephritis	Neg.	154	9
7	♀	55	Nephritis	Neg.	142	9
8	♀	60	Nephritis	Neg.	87	22
9	♂	50	Nephritis	Neg.	250	17
10	♂	45	Nephritis	Neg.	250	8
11	♀	47	Nephritis	Neg.	175	26
12	♀	49	Nephritis	++	307	11
13	♀	55	Nephritis	Neg.	222	15
14	♀	52	Arthritis deformans	Neg.	228	27
15	♂	38	Arteriosclerosis	Neg.	164	39
16	♂	62	Depressive insanity	Neg.	333	33
17	♂	27	Hemorrhagic retinitis	Neg.	200	40
18	♂	38	Hemorrhagic retinitis	Neg.	111	26
19	♂	30	Hemorrhagic retinitis	Neg.	181	16
20	♂	38	Exophthalmic goiter	Neg.	230	30
21	♀	34	Exophthalmic goiter	Neg.	185	30

TABLE 4.—MISCELLANEOUS CASES—(*Continued*)

Case	Sex	Age	Diagnosis	Wassermann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
22	♀	34	Exophthalmic goiter	Neg.	140	25
23	♀	34	Exophthalmic goiter	Neg.	166	44
24	♀	34	Exophthalmic goiter	Neg.	80	13
25	♀	34	Nervous and tired	Neg.	154	69
26	♂	45	Nervous and tired	Neg.	285	49
27	♀	55	Nervous and tired	Neg.	143	35
28	♀	55	Nervous and tired	Neg.	250	50
29	♀	38	Nervous and tired	Neg.	192	51
30	♀	40	Nervous and tired	Neg.	166	24.8
31	♀	52	Pyelitis	Neg.	146	22
32	♀	36	Pyelitis	Neg.	143	24
33	♀	36	Epilepsy	Neg.	111	35
34	♂	65	Cardiorenal disease	Neg.	142	38
35	♀	60	Cardiorenal disease	Neg.	147	31
36	♂	38	Headache (autointoxication)	Neg.	111	34
37	♂	41	Headache	Neg.	133	30
38	♀	48	Headache	Neg.	142	50
39	♂	55	Headache	Neg.	309	46
40	♂	40	Headache	Neg.	200	93
41	♀	45	Headache	Neg.	162	67
42	♂	30	Normal	Neg.	148	20
43	♀	56	Normal	Neg.	106	22
44	♂	53	Normal	Neg.	266	13
45	♀	27	Normal	Neg.	100	25
46	♀	23	Normal	Neg.	200	40
47	♀	25	Normal	Neg.	123	32
48	♀	25	Normal	Neg.	188	7
49	♀	25	Normal	Neg.	143	28
50	♂	60	Myocarditis	Neg.	166	24
51	♂	55	Tuberculous pleurisy	Neg.	133	53
52	♀	52	High blood pressure	Neg.	156	46
53	♂	35	Asthma	Neg.	145	36
54	♂	40	Prostate	Neg.	170	56
55	♂	45	Glaucoma	Neg.	153	22
56	♂	40	Glaucoma	Neg.	200	93
57	♀	50	Rheumatism	Neg.	166	47
58	♂	32	Rheumatism	Neg.	121	27
59	♀	50	Ulcer stomach	Neg.	154	49
60	♀	62	Tingling in fingers	Neg.	166	24
61	♂	35	Ureteral stone	Neg.	200	16

The nephritics have a retention of sugar depending on the severity of their lesion. The diastatic activity varies as in health.

In the case of arthritis deformans the patient had a general retention which was entirely corrected by diet.

The depressive insanity patient had a blood sugar of 333 and no glycosuria; it was probably due to diet and restraint in bed, and in his kidneys a high threshold of excretion for sugar.

The cases of hemorrhagic retinitis and glaucoma gave moderately increased blood sugars, and in one case, No. 56, an enormously increased diastatic activity.

Exophthalmic goiter cases gave high blood sugars, and indefinitely varying diastatic activity. Patients with pyelitis, cardiorenal lesion, epilepsy, myocarditis, tuberculous pleurisy, asthma, hypertrophied prostate, rheumatism and ulcer of the stomach, have normal blood sugar and normal diastatic activity.

The group of persons having no symptoms but those of overwork show a lack of oxidation of their sugar and at the same time a high diastatic activity. This may be traceable partly to an accumulation of unoxidized materials in the blood.

Eight normal persons were studied and each had normal blood chemistry, with the exception of two whose high blood sugar was purely dietary.

The blood sugar and diastatic activity are very variable, and up to the present their chief value lies in their definite relation to diet.

In our work we have had an opportunity to study nine eclamptics carefully (Table 5), and in this series there were no syphilitics. Glycosuria and hyperglycemia during the latter months of pregnancy are very frequent. These cases show only a moderate hyperglycemia, although it is at a time in pregnancy when one would expect the blood sugar to be much higher.

TABLE 5.—Cases of Pregnancy

Case	Sex	Age	Diagnosis	Wassermann	Blood Sugar, Mg. per 100 C.c.	Diastatic Function
1	♀	28	Eclampsia	Neg.	200	42
2	♀	27	Pernicious vomiting	Neg.	181	30
3	♀	29	Eclampsia	Neg.	165	27
4	♀	30	Eclampsia	Neg.	142	11
5	♀	28	Eclampsia	Neg.	184	20
6	♀	20	Eclampsia	Neg.	167	38
7	♀	26	Eclampsia	Neg.	160	25
8	♀	25	Eclampsia	Neg.	160	16
9	♀	26	Eclampsia	Neg.	125	25

The diastatic activity is normal in all except the first woman, who had a marked glycosuria.

The blood sugar and diastatic function behave very much as in the normal individual — affected by diet or renal insufficiency, but nothing else that is demonstrable in these few cases.

CONCLUSIONS

1. There is a low diastatic activity in diabetes associated with syphilis.

2. The internal secretion of the pancreas is probably inhibitory to the activity of the diastase in the blood.

3. Exposure to roentgen rays for either long or short periods of time does not alter the activity of the diastase, but in some cases temporarily lowers the sugar content of the blood.

4. There is nothing especially characteristic of either the blood sugar or diastase of the cancer patient at any stage of his disease.

5. Miscellaneous nondiabetic cases show normal sugar in the blood with normal or low diastatic activity; or high sugar with increased or low diastatic activity; but never low sugar with high diastatic activity.

6. The diastatic activity tends to increase with rising sugar in the blood, especially with a dietary glycemia.

7. In dietary correction of a hyperglycemia the diastatic activity decreases with the sugar, whether in a diabetic or not.

Further studies on the problem of diastase are in progress.

FATIGUE DISEASE

AS EXEMPLIFIED IN FUNCTIONAL DISORDERS OF THE STOMACH AND THYROID GLAND *

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The absorption and utilization of nutriment by a voluntary muscle is evidently dependent on the impulse conveyed in its motor nerve. Without that impulse, as after section and degeneration of the nerve, the muscle atrophies. The impulse, of course, performs its function, which thus must be, at least in part, trophic, at the distal extremity of the nerve or its end-plate. This, when the trunk of the nerve has been irritated by repeated electric shocks, can be readily made to cease functionation because of fatigue. When its onset is indicated by the decreasing contractions of the muscle, the intravenous injection of extracts of the thyroid, parathyroid and adrenal glands will immediately reinvigorate the failing contractions.[1] If, however, the fatigue of the end-plate is carried to the point of exhaustion, then these extracts become inert. In other words, the thyroid, parathyroid and adrenal glands probably pour into the circulation some material which produces a stimulating effect on the voluntary muscles through the intermediation of the nerve impulse at its point of discharge, or the motor end-plate. After the latter is destroyed, or ceases to functionate, neither food nor material derived from the thyroid, parathyroid or adrenal glands seems able to gain access to the muscle.

Unstriated, or involuntary muscle, as represented in the cat's uterus and different portions of the intestine, are believed to have a double nerve supply from the involuntary system. Irritation of one portion of this system produces contraction, and of the other relaxation. These contractions can be stimulated by extracts of several organs, including the thyroid and parathyroid glands. After the contractions have been thus started, they can be immediately inhibited or paralyzed by a 1:1,000 solution of epinephrin chlorid. The latter is accepted as having a selective stimulant effect on the terminal filaments of the sympathetic, and, therefore, because of its antagonistic action to the stimulating extracts, it is probable that the thyroid, parathyroid

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1. Am. J. Physiol. **45**:97 (Jan.) 1918.

and other organs produce their effect through either the terminals of the sympathetic or its opponent, the vagus system.[2]

It should be recalled that the involuntary nervous system, as noted, is composed of two parts, or groups, of nerves, and fibers from each are believed to supply every organ in the body except, so far as is known, the brain. This double innervation of all viscera apparently represents a regulating mechanism for controlling their interactivity. One set of fibers seems in general to activate the receiving cells, while the other, with the same distribution, inhibits them and, at the same time, produces vasoconstriction. The "activating" group, which may also contain vasodilating parts, is carried in the third, seventh, ninth, tenth and eleventh cranial nerves, and in the visceropelvic nerve (to the rectum, bladder and genitals), and has been designated by Langley as the autonomic system. It might be more easily identified under the name of its most prominent member, or as the vagus group or system. The inhibiting and vasoconstricting fibers are in the sympathetic with its cervical, thoracic and abdominal plexuses.

This double and apparently opposing or counteracting nerve supply of the viscera is most easily demonstrable in the stomach, in which the peristalsis and secretion are increased by electrical stimulation of the vagus, while both processes are inhibited by similar stimulation of the splanchnics. These same reactions can be excited in a more vigorous form and over a longer period by materials obtained from certain organs. That is, the subcutaneous injection (in dogs) of an alcohol extract, or of the noncoagulable part of a saline extract, particularly of the thyroid or parathyroid glands and of one or two other organs, or an acid decoction of the pyloric mucosa of the stomach (gastrin), will greatly stimulate the flow of gastric secretion. Extracts of the thyroid will increase this flow from five to ten times the normal amount, and decidedly increase the content of hydrochloric acid and the gastric peristalsis. The injection of atropin, which paralyzes the terminal filaments of the vagus, prevents or inhibits these (thyroid) reactions. The injection of a 1 : 1,000 solution of epinephrin likewise prevents or inhibits the stimulation by the thyroid and other organ extracts; but its action must be, as in the paralysis of the involuntary muscle contractions, through stimulation of the opponent of the vagus, or the terminal fibers of the gastric sympathetic, because epinephrin acts only on the sympathetic. This inhibition of the stomach activity apparently by the adrenal gland cannot be ascribed to the power of epinephrin to cause vasoconstriction, because none can be detected, and also because the adrenal nucleoprotein material which contains

2. Am. J. Physiol. **39**:154 (Dec.) 1915.

only traces of epinephrin, is very much more active than corresponding doses of epinephrin chlorid solution.

After both vagi are cut just above the diaphragm the quantity of the gastric secretion becomes reduced to about one-tenth of the normal, the stomach gradually dilates and is unable to empty itself, and the animal eventually dies, apparently of inanition. Before the general condition becomes bad, the injection of thyroid (and certain other stimulant organ) extracts is followed by practically no increase in the gastric secretion, but what little flow there is, is checked, as in the normal stomach, by the injection of epinephrin or of derivatives of the adrenal gland. That is, the stimulant extracts do not act, but the adrenal products still show their vigorous inhibiting power when the vagus has been destroyed and only the sympathetic is intact. Extracts of the pituitary show inhibitory effects which are similar to but less vigorous than those from the adrenal, and probably also act through the sympathetic, although this has not been definitely determined.[3]

All of the stimulant organ products, except possibly gastrin, seem thus to have an affinity for the terminal filaments of the gastric vagus and to intensify its apparent function. The products of the adrenal gland, on the other hand, and possibly also of the pituitary, have an affinity for, and intensify the apparent inhibitory power of the gastric sympathetic terminals.

Of all the functional disorders, those which involve the stomach and the thyroid gland are probably the most common, and they present many analogies and similarities. Each organ is supplied by the vagus and the sympathetic, each is subject to under- or overactivity and presumably to the same inhibiting and activating influences and their probable trophic accompaniments. Clinically, moreover, the corresponding functional disturbances in these organs occur and are intensified or relieved under the same general conditions in the same general type of "nervous" individuals.

A "nervous" person can be defined as one who responds to all stimuli with more than the usual rapidity and expenditure of energy, and in these responses, which are necessarily through the nerve terminals, fatigue should affect not only the motor end-plates, but also the involuntary or visceral nervous system. The latter is presumably subject to the same laws as the voluntary nerves, and though a fatigue and consequent defect or failure in functionation of the terminals of the gastric vagus or sympathetic has not been definitely proved, there can be little doubt of its occurrence. Certainly, if the experimental animal is angered or terrified, which is an emotion akin to worry, the

3. Am. J. Physiol. **39**:345, 1916; Ibid. **48**:79 (Feb.) 1919.

flow of its gastric secretion immediately ceases, and this has been proved to occur by inhibitory impulses conveyed to the stomach through its sympathetic nerve supply. When these impulses are long enough continued, the sympathetic terminals should suffer from a partial or complete fatigue failure, and the vagus would then be left to functionate without opposition. The result should be hypersecretion, hyperacidity and hypermotility or pylorospasm. These conditions are frequently encountered in nervous persons who have been subjected to fatigue and worry, and they are relieved by rest, presumably to permit the exhausted sympathetic terminals to regain their capacity to functionate. The usual medical treatment is by belladonna, which, of course, paralyzes the terminals of the apparently overactive vagus (although it is probably only unopposed), and by alkalis which, theoretically, at least, are more logical. For it is not impossible that alkalis, by neutralization of the excess of hydrochloric acid, prevent the formation of gastrin and a consequent autoactivation of the stomach.

As derivatives of the adrenal gland, experimentally, show vigorous gastric inhibition, their administration is logical. The most active of these products seems to be the nucleoprotein material. This can be obtained from an aqueous extract of the hashed fresh glands by precipitation with 10 per cent. acetic acid. The dose of the dried (nucleoprotein) powder is about 0.5 to 1 grain every two or three hours. Its effects are shown in the following rather abbreviated case history:

Case 1.—F. H., aged 27, a hospital orderly of the pronounced nervous type, complains for the past ten years of recurrent attacks of epigastric pain and distress which always come on after a period of night duty, especially when the service is active. The pain is slightly relieved by gas eructations and by "soda." After a few days, or rather nights, of hard work and worry the pain increases and awakens him during his sleeping period. With day duty and comparative rest the pain gradually subsides. Ewald test meal, Aug. 27, 1918, shows total acidity of 89; free acid 58. The roentgen ray at this time revealed hyperperistalsis and probable pyloric ulcer. Rest in bed, with the usual dietetic and medical treatment, resulted in no subjective improvement.

Sept. 11, 1918. Ewald test meal showed total acidity 93; free acid 54. Restriction in diet was then abandoned, and 1 grain of dried adrenal nucleoprotein material was given by mouth every two hours.

Sept. 25, 1918. The Ewald test meal showed a total acidity of 62; free acid 50, and the symptoms had disappeared. The patient returned to day duty and continued the adrenal proteins but avoided the fatigue of night work and up to the present writing (three months) remains well.

The commercial desiccated adrenal powder, or the 1:1,000 solution of epinephrin are, clinically and experimentally, not as efficacious in relieving hyperacidity and pylorospasm as the adrenal nucleoprotein material.

If the disturbance is severe and lasts long enough, it is, of course, regularly followed by ulceration. There is reasonable certainty that

acute ulcers of the stomach can be caused by bacterial infection, but in spite of Rosenow's demonstration of specific cocci in chronic ulcers, there is still some doubt as to their etiologic relationship. Infection may begin the process, but the cause of its continuation is obscure. If, however, the normal activity and quiescence of the stomach are dependent, as they seem to be, on the integrity of the organ's double nerve supply in conjunction with the secretions or products of other viscera, then any interference with this relationship, like a fatigue failure of the gastric sympathetic, might be followed by a defect in nutrition which should be localized in the region of greatest anemia, or where the muscular contractions are most pronounced. Hence there is still some reason for suspecting that gastric ulcer may have a trophic origin.

The cause of the chief subjective symptom, or the pain of this condition, is generally conceded to be due to spasm and not to the irritation by food or hydrochloric acid of the exposed surface of the ulcer. This spasm is, of course, dependent on the activity of the vagus nerve, which, in all probability, is "active" not because of some pathologic condition of the vagus, but because of a failure in function by its physiologic opponent, or the gastric sympathetic. The cause of this greater or less amount of functional failure in the sympathetic terminals is most reasonably explained by fatigue. This seems to involve some trophic, or both trophic and inhibitory influence exerted by the combination of the nerve impulse with the adrenal and possibly other organ products. When this balanced innervation, with its "nutritional" accompaniment, becomes impaired, as by a fatigue failure of the sympathetic, the unopposed action of the vagus should and evidently does result in hyperacidity and pylorospasm. In the experiments noted above, "gastrin" (made by boiling the pyloric mucosa in 0.4 per cent. hydrochloric acid) stimulates the stomach like extracts of the thyroid, and, therefore, in the presence of an excess of hydrochloric acid and in the absence of the restraining influence of the sympathetic, the stomach theoretically, at least, becomes auto-activated. The "gastrin," which presumably is formed by the action of the excess of hydrochloric acid on the pyloric mucosa, returns in the circulation to its source and continues the stimulation of the vagus or the gastric epithelium. This supplies the most reasonable explanation for the relief of symptoms which follows the administration of alkalis or the usual gastro-jejunostomy with the admission to the stomach of the alkaline pancreatic secretion. But this operation, with its relief of hyperacidity, or when there is no hyperacidity, does not always cure the pain which presumably means spasm. The explanation of its persistence or later occurrence, especially when no ulcer is present, must indicate not necessarily a fault in the hypothesis of gastrin auto-

activation, but a continuation of the original functional failure of the sympathetic. If the pain is due to a pyloric spasm, it should then be relieved by a pyloroplasty or Finney operation.

The following case history is illustrative:

CASE 2.—W. J., aged 32, a mechanic, decidedly of the nervous type, underwent a gastro-jejunostomy in June, 1917, for pyloric ulcer, which was not excised. Thereafter, his symptoms disappeared for several months. A year later, after a period of unusually hard work under trying circumstances, the same epigastric pain gradually returned. It was intensified by food, especially meat, and for the last month awakened him at night. The Ewald test meal showed a total acidity of 47; no blood. The roentgen ray revealed a patent and functionating gastro-jejunostomy, through which the bismuth meal rapidly passed. There was hyperperistalsis and, apparently, pylorospasm.

Oct. 5, 1918, exploration showed a perfect posterior gastro-jejunostomy and no adhesions about it or the duodenum. The latter contained in its upper curvature a thickened area which was apparently the former ulcer.

A 4-inch gastroduodenostomy, or Finney's operation, was then performed and no ulcer found. The previous gastrojejunostomy was not disturbed. Recovery was uneventful and the former distressing pain ceased and has not since recurred.

If, therefore, the spasm can be localized with reasonable certainty in the pylorus, even when no ulcer exists, a wide division of the circular muscular fibers at this point, as can be done by a Finney operation, is a logical mechanical treatment and is applicable under the proper conditions even when no ulcer is found. Doubt of the existence of an ulcer is often embarrassing, and prevents many useful and necessary operations because, when the ulcer is not present, experience has proved that the results of the usual gastro-jejunostomy are disappointing, and a simple exploration may not be regarded as justifiable. Therefore, the Finney operation in these cases is extremely useful, and is indicated when the epigastric pain cannot be relieved by the usual medical treatment (with adrenal feeding and rest) and is of enough severity and duration to impair the patient's working powers.

Excision of the ulcer whenever possible has been proved to be always expedient, and its removal when in the body of the stomach by transverse resection of the viscus is also logical because of the resultant, at least partial, paralysis of the gastric vagus. The subsequent defective functionation of this nerve with the consequent decrease of hydrochloric acid formation and muscular contraction, should relieve the apparent overactivity certainly of the distal portion of the gastric vagus. The division of the stomach apparently does not cause the complete paralysis of the organ which takes place in the experimental animal after vagus section in the thorax.

Rodman's operation of excision of the ulcer-bearing area serves the same purpose as transverse resection, so far as the functions of

the gastric nerves are concerned, but more radically and with greater risk.

The symptoms, then, at least of chronic gastric ulcer, are those of gastric hyperfunctionation, and the ulcer seems merely an incident and, although the complications, consequences and treatment of the ulcer are very important, it is apparently not the primary essential lesion which may be, not only a lack of balance in the innervation of the stomach, but also a hypofunctionation on the part of the chromaffin —or adrenal—sympathetic system. For the loss of flesh and strength, and the impairment of general vigor is out of all proportion to the supposed local cause. Furthermore, the benefit to be obtained by feeding some derivative of the whole adrenal gland, especially the adrenal nucleoproteins (and not epinephrin) is very suggestive.

To sum up the foregoing observations, it is reasonable to believe that the etiology of hyperfunctionation of the stomach, with or without ulcer, is not a "neurosis" or pathologic condition of the vagus, but a defect or failure in functionation in the gastric and possibly other parts of the sympathetic system, including the adrenal gland; that the ulcer is a secondary and incidental lesion; that the primary cause of the whole disturbance is a fatigue which interferes with the functionation of the sympathetic terminals, especially of the gastric sympathetic; that the symptoms are to be interpreted according to the functions of the involuntary nerves; and that the treatment, whether medical or mechanical, to be successful should constantly have these other abnormalities in view rather than the apparently secondary ulcer.

The acute gastric hypofunctionation is so constant and manifest an accompaniment of all extremes of fatigue that it is evidently traceable, like the condition in the voluntary muscles, to defective functionation in all the gastric nerve terminals. Presumably, when it becomes chronic, the activating or vagus terminals continue their defective functionation, and the result is a corresponding decrease in the gastric motility and secretion. The usual treatment is, of course, designed to stimulate and supplement these deficiencies, and because of its experimental specific activity, feeding with some thyroid preparation, especially an alcoholic extract, is usually of great benefit. At the same time, in connection with the apparent failure of the gastric vagus, it should be noted that the symptoms of hypofunctionation of the stomach and intestinal tract are also a part of the symptoms commonly accepted as those of hypothyroidism.

As asserted before, the functional disorders of the thyroid gland, like those of the stomach, are apparently of the same character and occur in the same type of "nervous" subjects. The exacerbations and remissions of these disturbances also occur under the same conditions

of fatigue, and the symptoms and pathologic physiology in both organs are mostly traceable to abnormal functionation by the involuntary nerves.

The function of the thyroid is generally conceded to be connected with oxidation, and the acceleration of metabolism throughout the body. The gland possesses this power through its product, which apparently activates the terminal filaments of the autonomic or "driving" portion of all of the involuntary nerves. For an alcohol extract or one in which there has been more or less hydrolysis, such as can be made by boiling (and filtering), a slightly alkaline saline extract, gives quite definite and immediate reactions.[4]

An extract made with distilled water, by the way, is inert. Thus a hydrolyzed or alcohol extract of the thyroid when injected into dogs appears to be vasodilator; a stimulant for the contractions of voluntary and involuntary muscles apparently through the terminals of their "activating" nerve supply; a stimulant in the same way for the stomach and pancreas (through the vagus) and also probably the salivary glands. But no material from either the normal or pathologic hyperthyroid gland will produce any appreciable degree of tachycardia. That is, so far as has been determined, extracts of the thyroid show no effect on the sympathetic or general inhibitory and vasoconstricting system, but do show a vigorous stimulating influence on the functions believed to be performed by the opposing group of nerve terminals, especially the vagus. The thyroid apparently "activates" the autonomic and not, as is generally believed, the sympathetic system. This corresponds with the majority of the typical symptoms which are accepted as indicating the existence of overactivity of the gland or hyperthyroidism. The flushed and moist or sweaty skin; the excess of the oral and salivary secretions; the pounding, and overacting (vagus) rather than the merely rapid (cardio-accelerator) heart; the good or excessive appetite (vagus hunger contractions); the frequent or loose bowel movements, are all signs, not of sympathetic but of autonomic or vagus activity.

The exophthalmos, which is not constant and may exist without any other evidence of hyperthyroidism, is generally believed to be due to irritation or stimulation of the sympathetic, but the mechanism by which it is brought about is unknown. The tachycardia, which is constant in hyperthyroidism, is traceable directly to the cardio-accelerator or a sympathetic nerve. But it cannot be produced experimentally within the usual laboratory period of two or three hours, although it can be brought about by feeding thyroid long enough to produce the usual acceleration of metabolism. Therefore, it seems

4. Am. J. Physiol. **48**:79 (Feb.) 1919.

probable that the simple rapid pulse which is so characteristic of hyperthyroidism is not due to the effect of the thyroid product on the cardio-accelerator nerve, but to the general metabolic activity. The overacting heart which is accompanied by a sensation of thumping or pounding, however, is probably dependent on the direct stimulation of the cardiac vagus by the thyroid secretion.

In contrast to the signs of autonomic stimulation which indicate hyperthyroidism, the opposite extreme of functionation, or hypothyroidism, is shown chiefly by a deficiency of autonomic activity. This closely simulates ordinary fatigue, and can only be differentiated from it by the presence of at least a perceptible thyroid enlargement and by the effects of thyroid feeding. Unfortunately the latter, because of the different action of different thyroid products, is uncertain.

To recapitulate then: the thyroid through its secretion apparently activates, not the inhibitory or sympathetic system, but all of the functions which are dependent on the impulses discharged through the vagus or autonomic terminals. As the vagus supplies the thyroid, the gland should, therefore, be "auto-activated." That is, the secretion returns to its source and gains access to the thyroid epithelium through its laryngeal, and so vagus, or presumably "activating" nerve supply. It is important to recognize this probability because of its bearing on the mode of action of thyroid feeding and of organ therapy in general. Certainly there are many cases of myxedema which cannot be cured in the usual way, or are made worse by thyroid feeding, and ultimately die from hypothyroidism. Cretinism, or congenital myxedema, is similarly disappointing, and even more "resistant" to thyroid feeding. It is also well known that complete extirpation of the thyroid (in man) is fatal.[5] These facts indicate that the patient who is benefited by thyroid feeding must possess a certain minimum amount of thyroid epithelium and it must be capable of more or less normal functionation. Otherwise the ingested thyroid material is inert or harmful. Evidently after passing through the digestive tract and the liver, this material emerges into the circulation, probably as an iodized amino-acid which, though it retains some affinity for the vagus terminals and experimentally may activate them, nevertheless, does not perform the full function of the normal thyroid product. That is, the ingested material, to be efficient, must first pass through the patient's own thyroid epithelium. If this epithelium or its vagus nerve supply, or

5. Some surgeons apparently believe that the entire thyroid gland can be removed with benefit to the patient in cases of hyperthyroidism. If later there did not follow the fatal cachexia thyreopriva which was proved by Kocher to be the result of this operation; then either the surgeon did not remove the entire gland or there must have existed some "aberrant" thyroid tissue.

both, fail to functionate, thyroid feeding is useless. There is some evidence which suggests that the nearer the medicament approaches in chemical structure that of the normal thyroid epithelium, the better is the effect; but even then, if the gland or its nerve supply is absent or inefficient, the feeding of any known thyroid product will not succeed. Probably all kinds of organ therapy are subject to the same general laws and, therefore, ovarian feeding, for example, after total oöphorectomy should be useless or nearly so.

The histologic changes in the thyroid alveoli which are characteristic of hyperthyroidism may occur diffusely and throughout the gland or be more or less localized circumferentially around an encapsulated cyst or adenoma. Under the latter conditions, it should be noted that the diseased tissue from which the superabundant secretion is supposed to proceed can practically all be excised by enucleation of the tumor, and the result is generally a complete relief from the hyperthyroid symptoms.

Any simple, or quiescent, goiter may, after the patient has been subjected to conditions which induce fatigue, be accompanied by signs of hypothyroidism or hyperthyroidism. Moreover, the same individual may at different times show signs which indicate opposite extremes of thyroid activity. That is, the functional thyroid diseases are interchangeable. Under conditions which insure rest, a moderate hyperthyroidism becomes regularly a hypothyroidism, but under fatigue, exophthalmos is usually added to the symptoms of hyperthyroidism. All of these disturbances, however, begin with a simple hypertrophy of the gland, which seems to be an enlargement to compensate for excessive demands on a possibly weak organ. The cysts, or adenomas, which form after the simple hypertrophy, are apparently incidents of the congestion, and may be reactions to a primary hemorrhage during this congestion for the promotion of glandular activity.

The functional thyroid diseases seem, then, to begin with a simple hypertrophy, which is accompanied by more or less marked evidences of hypothyroidism. These, it should be repeated, differ from the signs of fatigue only by the presence of the "goiter." From this primary stage of hypothyroidism the symptoms may advance into myxedema or into those of hyperthyroidism, and then finally into exophthalmic goiter. If recovery occurs, the symptoms "regularly" recede through these different stages, although the exophthalmos is generally the last abnormality to disappear. In many cases the development of hyperthyroidism occurs quite suddenly, but the number of those which follow the "regular" course is sufficient to indicate the probable origin of the disturbance. This is most reasonably explained by fatigue, or a condition which affects primarily the functions performed by the terminal filaments of all nerves, including those of the involuntary system.

The latter presumably control the functional activity of the thyroid as they do that of the stomach. If they did not so control it, any excess of thyroid product would immediately start and perpetuate a hyperthyroidism. For this gland, like the stomach, seems to be "auto-activated" through its vagus nerve supply. The restraining, or inhibitory, influences are probably dependent, as in the stomach, on the sympathetic or chromaffin system, which includes the adrenal gland (and possibly also the pituitary). It is worth noting, by the way, that the adrenals are believed, like the thyroid and stomach, to be supplied by filaments from both the vagus and the sympathetic. Therefore, if the thyroid-autonomic group activates, and the chromaffin system or the adrenal-sympathetic group inhibits, each viscus, then any overactivity of the thyroid should be met by stimulation of the adrenals and inhibition of the thyroid through its sympathetic nerve supply. If fatigue interferes with the functionation of the thyroid sympathetic filaments, as it seems to in the stomach, hyperthyroidism is inevitable.

The differential diagnosis between hypothyroidism and hyperthyroidism, because of the many mixed types of these disorders, is often clinically impossible. The most conclusive test of hyperthyroidism is furnished by the calorimeter, but it is not readily to be obtained. The histologic examination of an excised portion of the gland is definite when it includes the disease. Clinically, and in general, therefore, one must compare the signs which indicate autonomic or vagus activity with those which show their absence, or only the presence of impulses from the inhibiting sympathetic. If the evidences of autonomic activity preponderate in the form of more or less vigorous functionation in several organs as against the quiescence or inactivity of others, then the thyroid is probably overacting. If there is a general inactivity of the viscera, the condition is one of hypothyroidism. As mentioned previously, exophthalmos is by no means always a proof of hyperthyroidism; nor is a simple tachycardia which seems to be only a part of the general increased metabolism. A rapid pulse, by the way, is the regular accompaniment of extreme asthenia from any cause, and "weakness" is one of the most constant accompaniments of all thyroid abnormalities.

Some aid in the diagnosis can be obtained from a study of the history and the probable stage presented in the course of the disease. This is generally suggestive of some initial failure or deficiency, and, therefore, of a treatment which should conserve and "help out" the thyroid rather than destroy this evidently important gland. Hence, when the symptoms are not manifestly those of overactivity of the functions which are stimulated by the autonomic or vagus system, a cautious trial of "feeding" one or another thyroid derivative is rea-

sonable. Benefit, and even ultimate cure, can often be obtained in some cases of supposed hyperthyroidism by the administration, frequently repeated, of a few minims of an alcohol or a hydrolyzed extract of the thyroid; or $\frac{1}{100}$ or $\frac{1}{50}$ of a grain of the dried nucleoprotein obtainable by precipitation with 10 per cent. acetic acid from a saline extract of the hashed fresh gland; from $\frac{1}{20}$ to $\frac{1}{4}$ grain doses every three or four hours of the commercial desiccated thyroid powder is less often satisfactory. It is also reasonable, in cases of manifest hyperthyroidism, to attempt to reinforce the presumably weak or defective inhibitory or sympathetic-adrenal system by feeding some derivative of the adrenal gland. Epinephrin is clinically not as beneficial as an alcohol or a hydrolyzed extract of the whole gland, or as the adrenal nucleoprotein material (made like the corresponding thyroid nucleoproteins).

Surgery, however, has been abundantly proved to be the surest and safest treatment for all definitely hyperthyroid conditions. When the anatomic lesions which are characteristic of the disease can be localized with reasonable certainty in some particular portion or portions of the organ, their excision is curative. This localization can be determined with more or less accuracy because the hyperplastic alveoli lie, for the most part, closely around or in circumscribed tumors, and their enucleation or excision destroys or removes the source of the excessive secretion. Similarly, when the disease is probably confined to one lobe, as indicated by its greater size and density and vascularity, the removal of that lobe is generally indicated. Unfortunately, the lesion is most commonly scattered diffusely throughout the whole organ, as shown by its symmetrical hypertrophy and even consistency. Under these conditions, hemithyroidectomy is more apt partially or completely to fail than to succeed. The operation is designed to cut down the apparent excessive amount of thyroid secretion, and so check or stop the presumable "auto-activation." But the hyperplastic and hyperactive alveoli, even if they remain in much less than half the original gland, may continue the disturbance. I have seen at least one death with intensification of all the hyperthyroid symptoms after a practically complete thyroidectomy. Therefore, in view of these uncertainties, which apparently involve an extensive or general failure of the inhibitory apparatus as well as a theoretical local failure of thyroid inhibition, I advise the ligation, in two stages under local anesthesia, of all four of the chief thyroid vessels. The lower two can be easily reached behind the great vessels by an incision along the lower end of the posterior border of the sternomastoid, and should be tied first because there is practically none of the postoperative pain and consequent reaction which follows a wound nearer the pharynx. The object of the ligation operation is to cut off as

much as possible of the probable excessive "hormone" thyroid products which through the thyroid vagus terminals, seem to force the gland to overact. Practically, and especially if supplemented by some organ therapy, like adrenal or thyroid feeding, and always by rest, the quadruple ligation will cure all symptoms (except the protective or compensatory "goiter" [6]) in about 90 per cent. of the cases of hyperthyroidism, and with only a 2 per cent. or 3 per cent. mortality. But the recovery is generally slower than after partial thyroidectomy, and the continuation of a simple tachycardia even for weeks or months is not necessarily followed by a failure to cure.

This brief discussion of corresponding functional diseases in two apparently unrelated organs is intended chiefly to show the probable location of the primary lesion. This seems to be in the end-plates, or terminal filaments of nerves which have generally been regarded as of negligible importance. The experiments mentioned, though comparatively inadequate for any sweeping conclusions, are quite definite in showing the point at which one organ through its secretion can act on another. They thus suggest, if they do not prove, how normal physiologic processes may become pathologic. The mechanism of the function performed by the discharge of a nerve impulse, whether it belongs to the voluntary or the involuntary system, must be somewhat similar. It is undoubtedly chemical or physicochemical. The atrophy of a muscle after section of its nerve supply cannot be due to the absence of any mysterious "vital principle." In whatever manner the impulse may produce its effect, this effect is exerted at the nerve terminal. The latter's function, which is apparently much more than the mere discharge of an impulse, is well known to be affected by many poisons, and most definitely by fatigue, and this is by no means always the result of physical or rather muscular strain.

The ill-defined term of "nervous strain" means a restraint or inhibition of fear and the accompanying activating impulses to the organs which provide the energy to "run away" really or metaphorically. These impulses are conveyed to the viscera through the involuntary nerve terminals, and if these have in addition to, or in conjunction with, their activating and inhibiting powers, some "trophic" influence, which seems very probable, then one of the definite causes of disease, especially when it is among the disorders commonly designated as "neuroses," is fatigue.

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6. Am. Surg. **67**:447 (April), 1918.

THE PLASMA CHLORIDS IN ANEMIA: AN EXPERIMENTAL STUDY*

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The observations of Christian[1] on renal function in pernicious anemia, in which he found a disturbance in chlorid excretion, have suggested the study of the plasma and urinary chlorids in experimentally induced anemia in dogs. It was noted by Christian that urinary chlorid excretion in pernicious anemia, as measured by a two-hour renal test, approximated the characteristics of chronic nephritis. There was the same tendency to a fixation of urine chlorid percentage and impaired ability to concentrate the chlorids in the urine. These findings were not dependent on a concomitant nephritis or arteriosclerosis, and the disturbance lessened as the anemia improved. It was therefore pointed out by Christian that the presence of anemia as a factor would have to be considered in the interpretation of dietary renal tests on patients thought to have chronic nephritis. The determination of the plasma chlorid content was not taken up in his paper.

To produce an anemia of severe character and one lasting long enough to allow of repeated observations, dogs were infected with *Trypanosoma equiperdum*. The anemia of *T. equiperdum* infection in the dog has been studied by Krumbhaar.[2] He noted that signs of anemia appeared soon after the finding of trypanosomes in the blood. The fall in the hemoglobin at first took place more rapidly than the fall in the red cell count, but later was parallel to it. The hemoglobin may fall to 40 per cent. or lower and the red cells to 3,000,000 per cubic millimeter or less. Normoblasts and megaloblasts occasionally appear. There is evidence of blood destruction, as indicated by increased elimination of urobilin and increased storage of iron in the liver.[3]

The present study concerns itself with the determination of plasma and urinary chlorids in dogs suffering from the anemia of *T. equiperdum* infection in the absence of nephritis, and a single determina-

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1. Christian, H. A. Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests, Arch. Int. Med. **18**:429 (Oct.) 1916.

2. Krumbhaar, E. B.: Experimental Trypanosomiasis: T. Equiperdum Infection in the Dog, J. Infect. Dis. **22**:34 (Jan.) 1918.

3. Dubin, H., and Pearce, R. M.: The Elimination of Iron and Its Distribution in the Liver and Spleen in Experimental Anemia, II, J. Exper. M. **27**:479, 1918.

tion in an infected dog with induced uranium nephritis. We have at the same time had occasion to follow the uninterrupted course of the disease and have observed the various symptoms described by Krumbhaar. Emaciation and weakness occurred regularly. Stiffness of the legs, falling of the hair, keratitis, anorexia, vomiting and diarrhea were present in varying degrees, but the edema observed by some investigators, we did not see.

METHODS

Only dogs were used. They were placed on a constant diet of beef heart and cracker dust with sodium chlorid, 1 gm., every twenty-four hours. A number of preliminary determinations were made without the addition of the sodium chlorid to the diet. The plasma chlorids were determined by the method of McLean and Van Slyke.[4] The blood for this purpose was drawn from the jugular vein from twenty to twenty-four hours after the last feeding. The blood was collected under liquid petrolatum in centrifuge tubes containing crystals of potassium oxalate, immediately centrifuged and the plasma pipetted off. The urine for chlorid determinations was that obtained by catheterization from twenty to twenty-four hours after the last feeding and one hour after giving 100 c.c. of water by stomach tube. Determinations were made by the McLean and Van Slyke method as applied to urine.[4] These determinations were then indicated in the table as grams of chlorid per liter of urine. The amount of urine obtained by catheterization was added to the amount of urine collected in the bottle under the metabolism cage and was taken as representing the total volume of urine in twenty-four hours. The amount of chlorids for twenty-four hours was calculated on the basis of concentration represented in the catheterized specimens, though this did not allow for the varying concentration during the twenty-four hours. All chlorid determinations were made in duplicate.

After the dogs had been studied in a state of health, they were infected with trypanosomes by injecting into the jugular vein the citrated blood of a medium-sized rat, heavily infected with *T. equiperdum*. The blood was obtained from the rats by severing the vessels of the neck under anesthesia and allowing the blood to flow into warm sodium citrate solution (2 per cent. in distilled water).

The blood of the dogs was examined for the presence of trypanosomes in from about seven to ten days. Following their appearance and multiplication, anemia rapidly developed and became quite marked in the course of several weeks, or at times sooner, according to the severity of the infection. After the anemia had been definitely established, observations were again conducted on plasma and urinary chlorids and on renal function.

RESULTS

The results of determinations in normal dogs alone are given in Tables 1 and 2. These normal figures correspond to the findings of Austin and Jonas,[5] in the fact that the plasma chlorids are relatively high as compared to man, the urinary chlorids low. In Tables 3 and 4 are recorded the figures obtained with two dogs, first in a state of

4. McLean, F. C., and Van Slyke, D. D.: A Method for the Determination of Chlorids in Small Amounts of Body Fluids, J. Biol. Chem. **21**:361, 1915.

5. Austin, J. H., and Jonas, L.: Effects of Diet on the Plasma Chlorids and Chlorid Excretion in the Dog, J. Biol. Chem. **33**:91, 1918.

health and then after infection with *T. equiperdum*. In one of these a uranium nephritis was later produced in order to determine the effect of nephritis in the presence of anemia on the chlorids of the plasma and urine.

TABLE 1.—Normal Plasma and Urinary Chlorids

Dog 1.—Female; weight, 11,200 gm.; constant diet, minced beef heart, 300 gm., cracker dust, 50 gm., in twenty-four hours.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenolsulphonephthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlorids per Liter, Gm.	Chlorids in 24 Hours (calculated), Gm.	Albumin	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	6.12	350	1.0	0.35	0	0	....	....	.....	....
4	6.12	220	0.8	0.17	...	...	....	....	.....	....
6	6.0	250	1.5	0.37	...	...	....	....	.....	....
8	6.12	221	0.4	0.08	...	...	....	....	.....	....
10	6.25	235	0.6	0.14	0	0	50	10	5,460,000	92

TABLE 2.—Normal Plasma and Urinary Chlorids

Dog 2.—Female; weight, 11,000 gm.; diet, same as Dog 1.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenolsulphonephthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlorids per Liter, Gm.	Chlorids in 24 Hours (calculated), Gm.	Albumin	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	5.87	460	6.0	2.76	0	0	....	....	.....	....
4	5.60	255	4.1	1.04	...	...	....	....	.....	....
6	6.00	364	2.4	0.87	...	...	....	....	.....	....
9	5.87	378	3.4	1.28	...	...	....	....	.....	....
11	5.87	410	2.8	1.14	0	0	60	5	5,820,000	98

TABLE 3.—Plasma and Urinary Chlorids in Health and in Stage of Anemia from T. Equiperdum Infection

Dog 4.—Female; weight, 9,950 gm.; diet, beef heart, 250 gm.; cracker dust, 75 gm.; sodium chlorid, 1 gm. in twenty-four hours.

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenolsulphonephthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlorids per Liter, Gm.	Chlorids in 24 Hours (calculated), Gm.	Albumin	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	6.125	365	2.5	0.91	0	0	....	....	.....	....
3	6.0	420	2.2	0.92	...	...	....	....	.....	....
6	6.0	410	1.8	0.73	...	...	....	....	.....	....
8	6.125	540	2.1	1.10	0	0	65	10	7,250,000	110
				Period of Anemia						
37	6.50	620	3.1	1.90	0	0	....	....	3,050,000	40
39	6.50	710	3.3	2.30	0	0	....	....	.....	....
41	6.62	640	4.0	2.56	0	0	55	10	.....	....

TABLE 4.—PLASMA AND URINARY CHLORIDS IN HEALTH, IN STAGE OF ANEMIA FROM T. EQUIPERDUM INFECTION AND IN URANIUM NEPHRITIS

Dog 6.—Female; weight, 10,400 gm.; diet, same as Dog 4

Day of Experiment	Plasma Chlorids, Gm. per Liter	Urine					Phenolsulphonephthalein, per Cent.		Blood	
		Amount per 24 Hours, C.c.	Chlorids per Liter, Gm.	Chlorids in 24 Hours (calculated), Gm.	Albumin	Casts	1st Hour	2d Hour	Red Blood Cells	Hb., per Cent.
1	6.25	.....	.....	.....	...	...	....	....	.....	....
2	6.12	207	6.0	1.20	0	0	....	....	.....	....
5	6.37	520	2.1	1.09	...	...	....	....	.....	....
6	.....	331	3.2	1.05	...	...	50	15	.....	....
7	.....	510	3.8	1.90	0	0	....	....	6,050,000	98
				Period of Anemia						
25	6.75	430	5.1	2.11	0	0	....	....	2,850,000	50
27	6.87	451	3.3	1.41	...	...	....	....	.....	....
29	7.12	420	4.1	1.70	0	0	65	5	.....	....
	Period of Nephritis. Uranium nitrate, 0.02 gm., subcutaneously, given 31st day									
34	.....	430	1.1	0.47	Heavy cloud	Many gran.	....	....	.....	....
36	8.12	544	1.0	0.54	...	...	....	....	.....	....

The tables indicate that there was a constant and fairly marked increase in the plasma chlorids during the period of active infection and anemia. This is apparently not due to an impairment of chlorid excretion, as can be seen by the ample excretion of chlorids in the urine. It would appear desirable to have observations on the plasma chlorids in the anemias of man to throw further light on this question. Renal function as measured by phenolsulphonephthalein excretion shows practically no difference between the stage of infection and that of health. Neither albumin nor casts were found in the urine of the infected dogs. The single observation in Dog 6 on the effect of nephritis presents findings that could be expected as a result of the added factor of hindered excretion. Such impaired excretion is demonstrated in this case.

CONCLUSIONS

1. The chlorid concentration in the plasma is raised in the dog during the active stage of infection with *T. equiperdum* at the period when anemia is a prominent feature.

2. This increased concentration of chlorids in the plasma is not dependent on retention due to impaired capacity of the kidneys to excrete chlorids.

3. In one observation, uranium nephritis in a dog rendered anemic by *T. equiperdum* was followed by a still higher concentration of chlorids in the plasma associated with a definite impairment in the renal capacity for excreting chlorids.

4641 North Thirteenth Street.

THE CLINICAL SIGNIFICANCE OF SLIGHT NOTCHING OF THE R-WAVE OF THE ELECTRO-CARDIOGRAM *

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PITTSBURGH

As a result of extensive electrocardiographic studies in past years, the questions of the more common disturbances of the cardiac mechanism have for the time being been settled, and numerous investigators have directed efforts to the elicitation of electrocardiographic evidences of myocardial involvement. Carter[1] has summarized the knowledge of the aberrant beat and the electrocardiogram associated with a lesion of either branch of the atrioventricular bundle. The ventricular complex is said to be characterized by a notched or bizzare R-wave of high amplitude, a QRS interval exceeding 0.10 second and an exaggerated T-wave usually opposite to the initial deflection. Such curves are indicative of an extensive pathologic process and imply a grave prognosis. Oppenheimer and Rothschild[2] have described intraventricular or arborization block. The underlying pathology of their cases was coronary sclerosis or disseminated patchy sclerosis of the myocardium predominate in the Purkinje network. The electrical curves are of low voltage, the R-waves notched and the QRS interval exceeds 0.10 second. Robinson[3] has reported cases with abnormal ventricular complexes consisting of widened and notched QRS groups which he regarded as resulting from functional impairment of intraventricular conduction. Recently Neuhof[4] has set an arbitrary standard of 0.07 second for the upper limit of base line width of a normal R complex and presented cases with grave myocardial disease in which the R-waves measured from 0.07 to 0.12 second. He believes that such prolongation of R indicates myocarditis. (The width of the normal R-wave has been assigned different values by various authors: Lewis,[5] 0.03 to 0.04 second; Einthoven,[6] 0.03 second; Kraus and Nicolai,[6] 0.06 second; Oppenheimer and Rothschild give 0.10 second for the upper limit of normal.)

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1. Carter: Arch. Int. Med. **13**:803, 1914; idem. **22**:331, 1918.
2. Oppenheimer and Rothschild: J. A. M. A. **69**:429, 1917.
3. Robinson: Arch. Int. Med. **18**:830, 1916.
4. Neuhof: Arch. Int. Med. **22**:45, 1918.
5. Lewis: Heart **4**:242, 1913.
6. Quoted by Kahn: Ergebn. d. Physiol., 1914, p. 93.

DATA OF AUTHOR'S CASES

Case No.	Clinical Diagnosis	Rhythm	Type of Electrocardiogram	Leads Affected	R Complex	P-R Interval	Remarks
1	Syphilitic myocarditis; nephritis	Atrial fibrillation	Left Vent.	L III	R III 0.06	—	Death
2	Myocarditis; aortitis; emphysema	Atrial fibrillation	Normal	L III L II L I (sl.)	R I 0.08 II 0.07 III 0.08	—	Death
3	Syphilitic myocarditis; nephritis	Normal	Right Vent.	L III	R III 0.065	0.22	Death
4	Rheumatic myocarditis; mitral disease	Atrial fib.–rillation	Left Vent.	L III	R I 0.06 II 0.08 III 0.08	—	Death
5	Rheumatic myocarditis	Atrial fibrillation	Normal	L I L III	R I 0.07 II 0.08 III 0.05	—	
6	Rheumatic myocarditis; nephritis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.08	0.165	Recurrent tonsillitis and arthritis
7	Myocarditis; arterio-sclerosis	Premature beats	Left Vent.	L III	R I 0.04 II 0.06 III 0.07	I 0.16 II 0.16 III 0.20	Subject to anginal attacks
8	Nephritis; myocarditis; syphilis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.06	I 0.16 II 0.18 III 0.18	Later admitted with atrial flutter; death
9	Syphilitic myocarditis; nephritis	Normal	Left Vent.	L III L II L I	R I 0.07 II 0.07 III 0.06	I 0.14 II 0.15 III 0.16	
10	Rheumatic myocarditis; mitral disease	Normal	Normal	I, II, III	R I 0.06 II 0.06 III 0.05	I 0.12 II 0.14 III 0.16	
11	Syphilitic myocarditis; aortitis	Normal	Left Vent.	L III	R I 0.07 II 0.07 III 0.07	I 0.14 II 0.16 III 0.16	Death later from bronchopneumonia
12	Rheumatic myocarditis; pericarditis; mitral disease	Premature beats	Normal	L III	R I 0.05 II 0.08 III 0.08	I 0.17 II 0.18 III 0.18	Atrial premature beats constant; inverted P in L III
13	Syphilitic aortitis; aneurism; myocarditis	Normal	Left Vent.	L III	R I 0.07 II 0.08 III 0.08	I 0.14 II 0.16 III 0.16	Chancre 3 years ago
14	Myocarditis; arterio-sclerosis	Normal	Left Vent.	L III	R I 0.06 R II 0.06 III 0.07	I 0.18 II 0.22 III 0.18	No cardiac symptoms
15	Rheumatic myocarditis; mitral disease	Normal	Normal	L III L II	R I 0.07 II 0.07 III 0.07	I 0.22 II 0.22 III 0.22	Acute appendicitis; no cardiac symptoms
16	Myocarditis; arterio-sclerosis	Atrial fibrillation	Left Vent.	L I L III	R I 0.06 II 0.05 III 0.06	—	
17	Chronic myocarditis	Atrial fibrillation	Left Vent.	L I L III	R I 0.08 II 0.07 III 0.08	—	
18	Myocarditis; arterio-sclerosis	Atrial fibrillation	Left Vent.	L I L II	R I 0.07 II 0.07 III 0.04	—	Chronic alcoholism
19	Chronic valvular disease; mitral; aortic; pericarditis	Normal	Normal	L I L III	R I 0.06 II 0.08 III 0.08	Average 0.20	Etiology, rheumatic fever
20	Cardio-sclerosis	Normal	Left Vent.	L III	R I 0.06 II 0.06 III 0.06	Average 0.20	
21	Chronic valvular disease, mitral	Normal	Right Vent.	L I L II	R I 0.07 II 0.07 III 0.05	Average 0.17	No cardiac symptoms; etiology not known
22	Syphilis	Normal	Left Vent.	L III	R III 0.04	I 0.12 II 0.16 III 0.10	
23	Syphilis	Normal	Left Vent.	L III	R I 0.07 II 0.08 III 0.07	Average 0.14	
24	None made	Normal	Left Vent.	L III	R I 0.06 II 0.07 III 0.06	I 0.11 II 0.12 III 0.10	Attacks of tachycardia

DATA OF AUTHOR'S CASES—(*Continued*)

Case No.	Clinical Diagnosis	Rhythm	Type of Electrocardiogram	Leads Affected	R Complex	P-R Interval	Remarks
25	Chronic nephritis	Normal	Normal	L III	R I 0.04 II 0.06 III 0.06	III 0.16	
26	None made	Normal	Normal	L III L II	R I 0.08 II 0.05 III 0.08	Average 0.14	Attacks of premature beats and precordial pain
27	None made	Normal	Left Vent.	L III L II	R I 0.07 II 0.08 III 0.06	I 0.14 II 0.16 III 0.16	Palpitation; B. P., 140-110
28	Syphilis	Normal	Normal	L III	R I 0.06 II 0.07 III 0.07	I 0.16 II 0.16 III 0.16	
29	Not made	Normal	Left	L III	R I 0.04 II 0.07 III 0.08	I 0.14 II 0.17 III 0.17	Palpitation; systolic pressure 160 at times
30	Not made	Normal, except for premature beats	Normal	L I	R I 0.06 II 0.07 III 0.07	I 0.12 II 0.14 III 0.14	Slight precordial pain at times; premature beats, atrial constantly present

An examination of the literature of the past eight years with reference to that point reveals ample evidence, based on experimental, pathologic and clinical studies, for regarding variations in the QRS group as due to structural or functional changes in the main bundle, the principal branches or the ramifications of the Purkinje network.

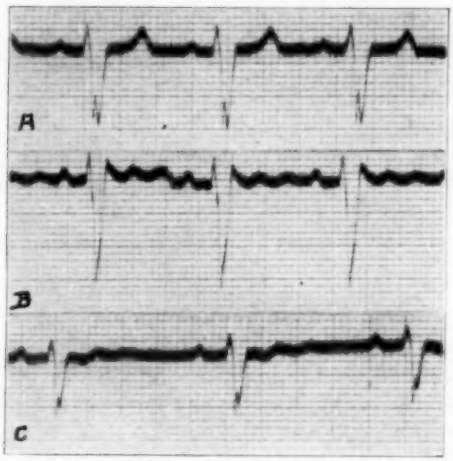

Fig. 1.—A, on admission; B, after 30 c.c. of digitalis; C, after 80 c.c.

The purpose of this paper is to call attention to slight notching or localized thickening of the R-wave, and by correlation of this with other abnormalities of the electrocardiogram when they are present, and with the clinical findings, to endeavor to establish a basis for its

significance, and to postulate its possible value as an evidence of myocardial involvement when that is the principal deviation from the normal that is found in the electrocardiogram and when physical examination affords no positive evidence of invasion of the myocardium.

The accompanying table comprises in a general way three groups of cases: those with severe myocardial disease, readily recognizable clinically, in many of which atrial fibrillation was present; a second group, less severe clinically, but including cases in which a diagnosis of myocarditis was justifiable; and a smaller number in which the history or certain physical signs suggested the possibility of myocardial disease, although there had never been any failure of cardiac

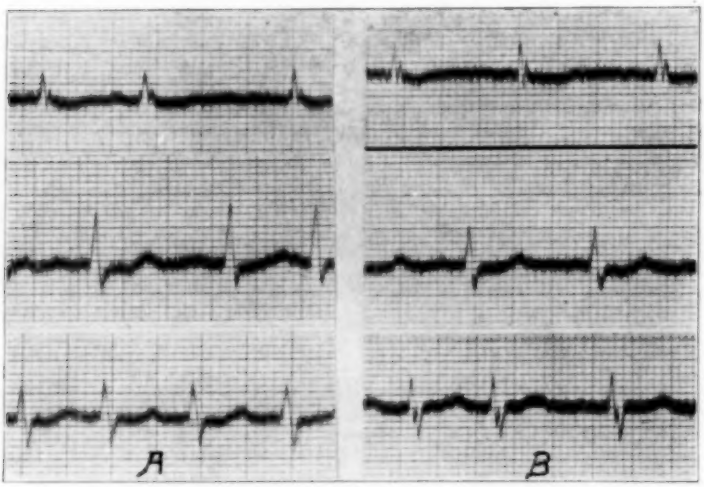

Fig. 2.—Case 4. A, Jan. 20, 1916; B, Oct. 14, 1917.

reserve, or, in a few cases, any symptoms referable to the heart. The cases of known etiology in which this notching has been observed have rheumatic infection, syphilis or arteriosclerosis as the causative factors of the cardiac disease.

The discussion is limited to R complexes of base line width of less than 0.10 second. In the majority of cases cited the notching occurred only in the third lead, or was usually more marked in that lead when present in others. In about one-half of the cases the electrocardiogram was of the type associated with left ventricular preponderance. These facts make the presence of such notching of special value in judging the left heart. In many cases there was no

appreciable prolongation of the P-R interval; occasionally it was prolonged only in one lead, the third, or less frequently the second, usually in association with the greatest degree of notching.

The notching has been observed in a few cases to increase in degree. This is believed to indicate an extension of the pathologic process

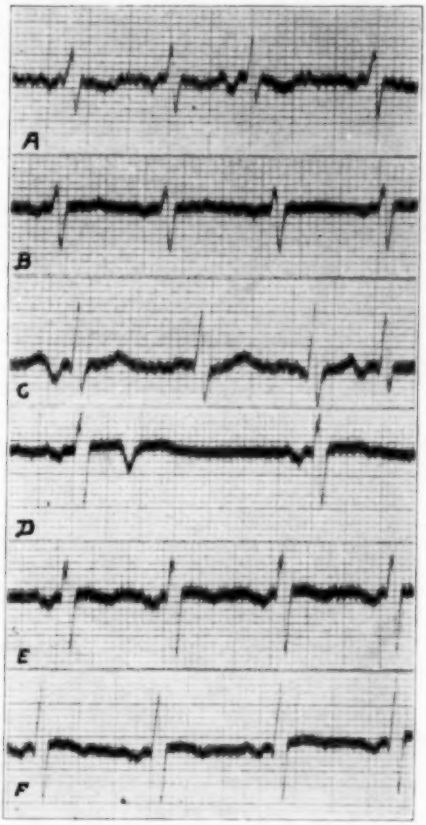

Fig. 3.—Case 12. Lead III. A, June 6, 1917; B, June 16, 1917; C, Oct. 24, 1917; D, March 28, 1918; E, April 25, 1918; F, June 2, 1918.

(Case 4). On the other hand, the notching may be transient or decrease under conditions that favor functional improvement in the conducting system (Case 12). Changes may be produced by digitalis; Figure 1 is interpreted as showing, first, improvement, and later, depression of the conducting system by that drug. That the notching may decrease or disappear in cases of syphilis following treatment is

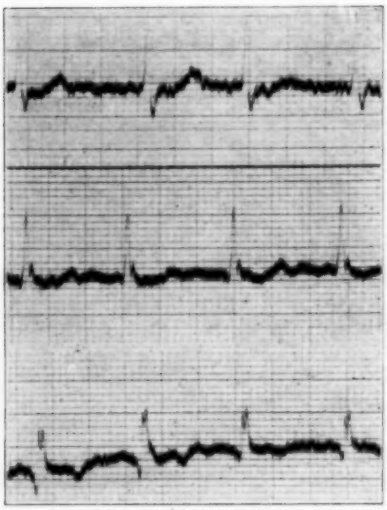

Fig. 4.—Case 2.

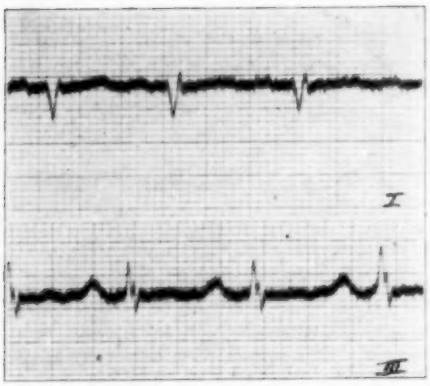

Fig. 5.—Case 3.

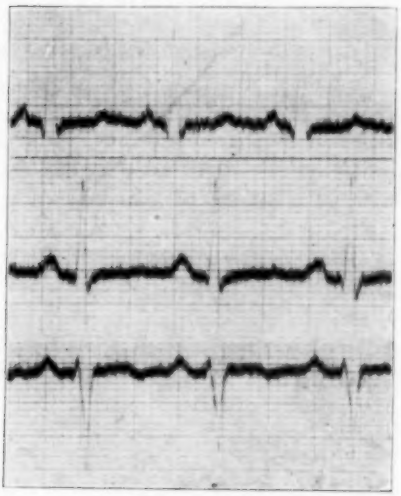

Fig. 6.—Case 6.

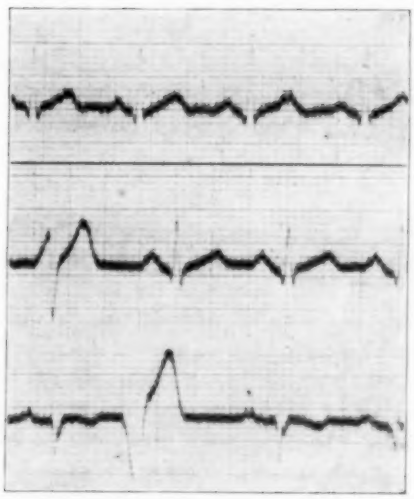

Fig. 7.—Case 7.

conceivable, although it has not been observed in any of the cases studied.

There was no quantitative relation between the notching and the clinical signs or symptoms, and it was not always present in what appeared otherwise to be similar conditions. It is not of definite value in prognosis, but it is believed, however, when constantly present in any given case, to indicate slight architectural changes, fibrotic in nature, in the finer ramifications of the intraventricular conducting system.

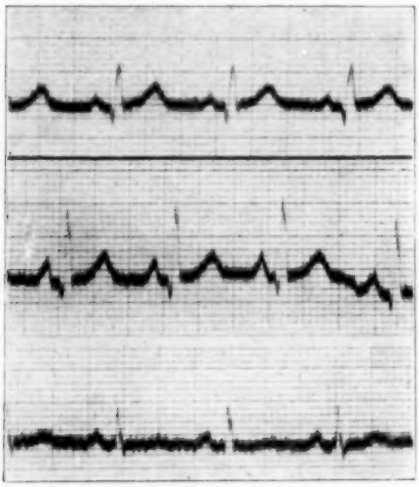

Fig. 8.—Case 10.

SUMMARY

Slight notching or localized thickening of the R complex of the electrocardiogram is frequently encountered in cases of unquestionable myocarditis. It often occurs in the third lead only, and in the majority of cases is associated with left ventricular preponderance. It may be present in an otherwise normal electrocardiogram, and is seen in cases in which physical examination affords but little evidence of myocardial disease. While no quantitative value can be assigned to such notching, it is believed, when permanent, to indicate pathologic changes in the myocardium, and when transient to reveal a temporary or potential defect in the conducting system, and is thus of aid in differentiating purely valvular lesions or functional affections of the heart. Illustrative cases are cited.

REPORT OF CASES

CASE 4 (Fig. 2).—Mrs. W. F., aged 57 years. This patient was admitted to the hospital four times during the previous two years, each time presenting marked cardiac decompensation. There was a history of repeated attacks of rheumatic fever. The clinical diagnosis was myocarditis, chronic valvular disease, mitral stenosis and insufficiency, and atrial fibrillation. Compare "A" and "B," Figure 2.

CASE 12 (Fig. 3).—T. L., a boy of 16 years. When first admitted, June 4, 1917, he complained of pain in the chest, weakness and fever. This illness was preceded by sore throat. He said that he had been unwell during the previous year and also that four years previously he had been in a hospital in Austria, but did not recall anything about the trouble at that time. The clinical diagnosis made was: chronic mitral endocarditis and chronic peri-

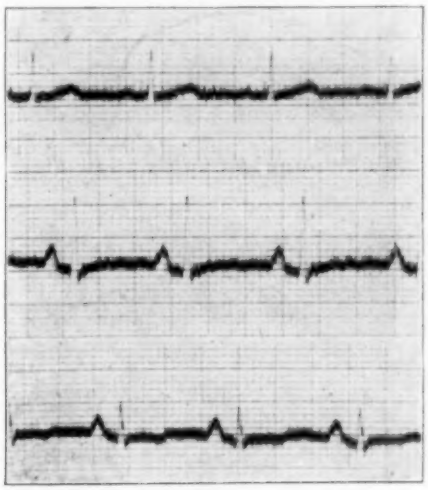

Fig. 9.—Case 25.

carditis, rheumatic in origin. The cardac rhythm was disturbed by many premature beats arising in the atrium. (See "A" and "B," Fig. 3.)

The second admission was in August, 1917, because of pain in the heart. He improved and left the hospital after fifteen days.

Sept. 20, 1917, he again entered the hospital, this time suffering from acute rheumatic fever involving the right knee, shoulder and ankle joints. Records taken at this time showed short paroxysms of tachycardia. Slight notching of R in the second and third leads is seen (Fig. 3, "C").

March 28, 1918, he returned to the hospital with acute bronchitis. The notching was more marked at this time (Fig. 3, "D" and "E").

A record taken two months later, after he had left the hospital, showed the notching much diminished, although still present (Fig. 3, "F").

CASE 2 (Fig. 4).—M. D., aged 66 years. This woman told of having suffered from heart trouble, shortness of breath and attacks of asthma for the previous five years. There was no history of rheumatism or syphilis.

Marked emphysema and bronchitis were present. The heart was enlarged; the sounds were weak but unaccompanied by murmurs; atrial fibrillation was present. Blood pressure, 145-100. Death occurred suddenly.

At necropsy the heart weighed 510 gm. The muscle cells showed moderate hypertrophy. There was a calcified area at the left edge of the mitral ring. In the aorta were numerous calcified plaques and the intima showed atheroma.

Case 3 (Fig. 5).—B. B., colored, aged 40 years. This patient had been admitted several times during the previous two years. The clinical diagnosis was syphilitic myocarditis and nephritis. The heart was enlarged both to the left and to the right. There was a systolic murmur at the apex. Blood pressure, 140-115. The urine contained albumin and casts; the phenolsulphonephthalein output for two hours was 30 per cent. Shortly after the last admission, Nov. 16, 1917, death occurred.

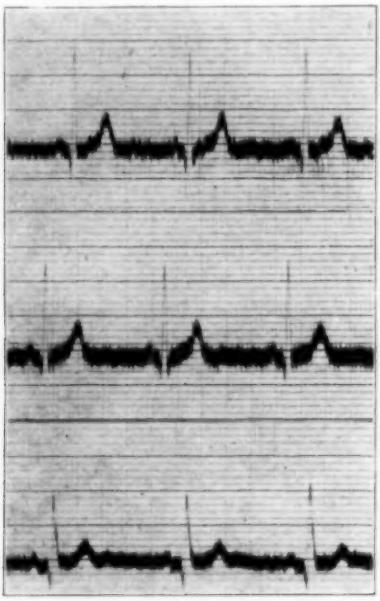

Fig. 10.—Case 28.

At necropsy, the heart weighed 785 gm.; the left heart was enlarged and the right heart distended. The papillary muscles were hypertrophied and sclerosed and there was a generalized fibrosis of the myocardium. The coronaries were thickened. The muscle elements showed hypertrophy and the striations could not be made out.

Case 6 (Fig. 6).—M. A., colored, aged 50 years. This patient was admitted Oct. 11, 1917, and remained about six months. There was a history of repeated attacks of rheumatism and tonsillitis; she had several while in the hospital, and in addition, one attack of erythema nodosum. The tonsils were definitely pathologic. The heart was enlarged to the left, the left border being at the anterior axillary line; no murmurs were heard. The pulse was irregular in volume. Premature beats were present at different periods. Blood pressure, 168-98. The urine contained albumin and at times red and white blood cells.

CASE 7 (Fig. 7).—F. E., aged 57. This man had been seen several times during the previous two years. He suffered from attacks of dyspnea and occasional fainting spells. During recent months he had had numerous anginal attacks, with pain referred to the left arm. The heart was not enlarged to percussion. A systolic murmur was heard over most of the precordium. The aortic second sound was accentuated. Premature beats were present during every examination. Blood pressure, 118-75. The urine was negative.

CASE 10 (Fig. 8).—A. S., aged 42 years. On admission, the patient complained of shortness of breath and pain in the chest, of two months' duration. He had rheumatism twenty years previously and heart trouble nine years previously.

There was slight enlargement of the liver, and moderate edema of the ankles which disappeared promptly. The left border of cardiac dulness was at the midclavicular line; the right border, 3 cm. to the right of the sternal

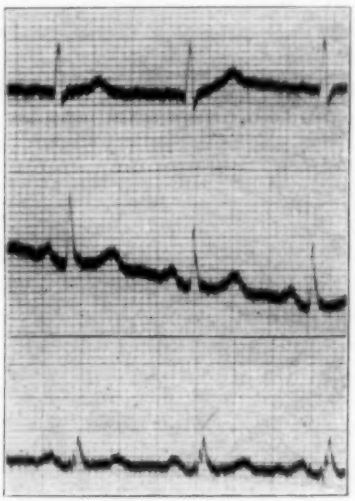

Fig. 11.—Case 26.

margin in the third and fourth spaces. The first sound at the apex was entirely replaced by a murmur which was transmitted to the axilla. Blood pressure, 110-70.

CASE 25 (Fig. 9).—J. Y., aged 43 years. While at work in a foundry the man became suddenly ill, with vomiting, abdominal cramps, diarrhea and pains in the muscles of the back and legs. Vomiting continued for several hours after he was brought to the hospital. Afterward he showed no symptoms during the six days he remained. He attributed his trouble to some pork that he had eaten for breakfast. The previous history was negative.

There was slight but persistent cyanosis. The knee jerks were sluggish; the examination of the nervous system was otherwise negative. The heart was not enlarged to percussion; the sounds were somewhat feeble; no murmurs were heard. The brachial and radial vessels were sclerosed. Blood pressure, 120-84 to 94. The urine contained a trace of albumin and hyaline and granular casts.

CASE 28 (Fig. 10).—N. R., aged 31 years. This man came into the dispensary complaining of headache, pains in the legs and transient tingling or prickling sensations in various cutaneous areas. There was a definite history of gonorrhea and of syphilis; no history of rheumatism.

The heart showed no enlargement and the sounds were normal except the aortic second which was distinctly accentuated. Blood pressure, 116-76. Blood Wassermann, two plus. Spinal fluid, negative.

CASE 26 (Fig. 11).—J. H., aged 38 years. This was a referred patient who was seen but once at the laboratory. He complained of attacks of palpitation at intervals of from six weeks to three months during the previous two years. These attacks occurred while at rest, usually at night. Simultaneously there was slight precordial pain, not referred to shoulder or arm, and without cutaneous hyperesthia. He had suffered from asthma for the previous twelve years. There had been excessive use of chewing tobacco for twenty years.

The heart was not enlarged to percussion. The sounds were clear, not accentuated and unaccompanied by murmurs. The pulse rate was 78; the blood pressure, 132-80. Over the lungs occasional sibilant râles were heard and expiration was prolonged.

The first impression was that there was a large nervous element in this patient's distress. But the notching and slight prolongation of R in the third lead, and to a lesser degree in the second, of an otherwise almost normal electrocardiogram when considered in the light of other cases suggests greater myocardial involvement than is obvious from the physical signs and indicates a more plausible cause for those symptoms of which the patient complained.

St. Francis Hospital.

FATIGUE IN IRRITABLE HEART AND OTHER CONDITIONS *

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First Lieutenant, M. C., U. S. Army
LAKEWOOD, N. J.

There is no more constant complaint among men suffering from the irritable heart of soldiers than that of fatigue. In civil life these men learned to adapt themselves to a low economic level by acquiring positions in which they could earn a living with the minimum of endeavor. Apparently the fatigue is of so real a nature to them that, to avoid it, they renounce most of the games and pleasures indulged in by the growing boy. In the army these men meet first their old enemy, physical exertion, without preliminary training, and with physique usually entirely inadequate to the demands. A considerable percentage do practically no duty, collapsing under the first "hike"; it is with this group that the work at Lakewood has largely dealt. Still others with this condition struggle through the training period, only to break down under the strain of battle conditions.

This work was undertaken with the purpose of finding some index to the degree or to the nature of this fatigue. Ryan[1] has observed that general fatigue exerts an influence on the white vasomotor reflex which is produced by stroking the skin with a blunt edged instrument. He showed that activity or loss of sleep causes a measurable shortening of the time interval between the appearance and fading of the white line that appears on the skin after such a stroke. Ryan constructed a simple spring instrument with which a stroke can be made by a blunt edge of wood under any desired pressure. His kindness in furnishing us such an instrument made this work possible.

The fatigue of which patients with the symptom complex of irritable heart complain is not limited to certain muscle groups. It is a general and frequently an overwhelming sensation. They often sit abject wherever they find themselves at the end of their exercises or throw themselves on their beds as soon as they can make their way to their wards. This study is concerned with general fatigue, and this symptom is largely responsible for the military disability of men with the irritable heart.

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* From the U. S. Army General Hospital No. 9.

1. Ryan, A. H. (with the collaboration of J. H. Gordon): Proc. Soc. Am. Phys., December, 1917.

Ryan made his observations on five healthy nurses. He made readings of the duration of the vasomotor reflex at various times of day over a considerable period. He demonstrated that the duration time of the vasomotor reflex was shorter after a day's work than it was in the morning. He has, therefore, introduced this test as an index to general fatigue.

The white vasomotor reflex is well described by Longet,[2] who refers to previous observations by Marey.[3] Longet describes the phenomenon as follows: "By stroking the skin with a blunt instrument, one sees first a white line from mechanical stripping; then, twenty or thirty seconds later, the white persistent line appears. This line differs from that made with a sharp instrument, which has a red center and white edges." This description agrees with the observations made at Lakewood, with the exception that the "latent period," the time between the stroke and the appearance of the persistent white line, has often been as short as ten seconds.

The nature of the phenomenon is not easy to determine. Vulpian[4] says, "The phenomenon bears chiefly on the arterioles of the stimulated region, which are richly supplied with muscle fibers. These probably contract, forcing the blood into the capillaries. The capillaries then become blanched, being pressed on by the elasticity of the surrounding tissues, while no blood reaches them from the arterioles." Vulpian considered that, in addition to the muscular factor, the vasomotor apparatus is brought into play in the production of this phenomenon, because the appearance of the white line is not immediate. Whether there is a vasomotor element or not it is difficult to say, for the evidence from the literature does not carry us beyond the muscular factor. The effect of fatigue in shortening the duration of the line is probably exerted exclusively on the muscular apparatus, as nerve fibers are known to be unchanged by any stimulation short of the most prolonged, while smooth muscle is readily fatigued. Lee[5] says, "While nerve is probably not indefatigable, it is extremely resistant in comparison with other peripheral tissues." The same writer[6] tells us, from observations on skeletal muscle, that the depressing action of fatigue substance is exerted on the muscle protoplasm itself. Howell[7] concludes that local fatigue is due to the elaboration of lactic acid, carbonic acid, and possibly acid potassium phosphate, and that the effect is probably due to the acidity of the products formed.

2. Longet, A.: Traité de Physiologie **2**: 1869.
3. Marey: Ann. des Sciences Nat. Zool., Series 4, **9**:68.
4. Vulpian: Physiologie et Pathologie du l'Appareil Vaso-Moteur, p. 46.
5. Lee, F. S.: J. A. M. A. **46**:1491 (May 19) 1906.
6. Lee, F. S., Am. J. Physiol. **20**:170, 1907.
7. Howell: Textbook of Physiology, W. B. Saunders Co., Philadelphia and London, Ed. 7, 1918.

It seems, therefore, that we are dealing with a muscular or neuromuscular phenomenon of the peripheral vascular system, the duration of which is shortened following activity or loss of sleep, and that the direct cause of such shortening is probably the action of acid bodies on the vascular musculature.

While the test is local, it is affected by general bodily activity and is an index to the subject's sense of general fatigue.

The Test.—The test is performed in a darkened room. The subject exposes the anterior surface of the forearm, against which the concentrated rays of the 25 W. Mazda bulb are directed. A black background is very helpful, in resting the observer's eyes and in increasing the definition of the area to be observed. The Ryan instrument is grasped, and the wooden marking disk is pressed on the subject's forearm until the standard pressure (90 gm.) is indicated. This pressure was the same in all the tests. Then two strokes are made, without changing the pressure, across the forearm as rapidly as feasible. A stop watch is snapped at the end of the first stroke. At from ten to thirty seconds white lines appear where the strokes were made. The watch is snapped, read, and restarted, with the loss of only a fraction of a second. The first reading indicates the "latent period." As soon as the first indication of blushing of the white lines sets in the watch is again snapped: this second reading is the "duration time," and it is, according to Ryan, the more variable and significant figure.

By the foregoing technic the vasomotor phenomenon is practically always a pure white; in this respect it differs from the reaction obtained with a sharp instrument, when a red line is characteristically seen in the middle of the white reaction. In only one of several hundred tests made at Lakewood was a red vasomotor reaction (the common "tache") seen. In this instance the red line appeared in a few seconds, and no secondary white reaction could be seen; on repeating the test immediately after exercise a pure white reaction, of the usual type, was obtained. This observation was interesting, because it showed that there is a direct effect on the vasomotor system from even light general exercise.

Certain precautions were rigidly adhered to in performing this test, with the purpose of eliminating as far as possible the element of personal error in reading the reaction. If the observer is making a series of observations on the same individual, he should have no knowledge of previous readings; if he knows, for instance, that a reading of thirty seconds had been made an hour before he will unconsciously expect subsequent readings to be at about the same time. To avoid this, all the readings made at Lakewood were dictated to a clerk, who alone was aware of previous figures. The room in which the observations were made was always warm enough to prevent chilling; if the subject is not comfortably warm, the skin is not pink enough to show a satisfactory reaction. Moreover, a blanched skin is apt to be made pinker by exercise, and, if readings are made before and after exercise, an element of error is introduced on account

of the altered color of the skin. It was found that the test is very unreliable in the case of Jewish patients, probably on account of the usually sallow complexion of the skin, which furnishes an unfavorable background for the reaction. In the case of several men of this race no reaction whatever could be seen; in others, it was indistinct, and, in still others, the figures were so bizarre, that they must have been due to errors in reading the tests. For these reasons all figures obtained from tests on Jews were uniformly eliminated from the calculations here reported.

The Day Curve.—The first observations were on the day fatigue curve. Readings were made on fifty-four men at 8: 30 a. m., 11 a. m. and 5 p. m. These men were all subject to similar routine. There were exercises before the first reading. There were also exercises at 4 p. m., but there was an average rest period of one hour between the afternoon exercises and the last reading. During the day the men were occupied with various light duties in the educational department, none of which was really fatiguing, and by walking or resting at their pleasure. The men for the test were taken from the cardiac wards. After the readings were made, they were grouped according to the clinical diagnoses of the patients, and the average days curves of the various groups of patients were calculated. They are shown in Chart 1. The diagnoses physically inferior, constitutionally inferior, emotionally sensitive, and neurotic are applied to groups of patients who have the syndrome of irritable heart; these subdivisions are based on suggestions made by Campbell[8] from a study on the patients with cardiovascular disorders at this hospital. The organic group represents all patients with demonstrable organic disease of the heart. The post-infection group contains those patients who develop the symptoms of irritable heart after an acute infection, but in whom no organic disease of the heart can be demonstrated. Chart 1 shows nothing striking. There is a general correspondence among the curves; the more marked fatigue occurs between the latter two readings, except in the case of the group of physical inferiors. The most marked fatigue occurred in the emotionally sensitive group; this was again the case when readings were subsequently made just before and after exercise. In all groups the evening reading was shorter than the morning.

Fatigue by Exercise.—In order to make a quantitive estimate of the fatigue produced directly by physical exercise among men with irritable heart, readings were made in fifty-four cases just before and after exercise. The figures were again grouped according to clinical

8. Campbell: J. A. M. A. **71**:1621, 1918.

diagnoses, and the results are shown in Chart 2. The first reading was made between 3 and 4 p. m.; at 4 o'clock the men had light "setting-up" exercises, at the end of which they reported for the second test. These results have particular bearing on the subject of fatigue in men with irritable heart. This general diagnosis includes Groups A, B, E, F, G and I in Chart 2. In Group K are two cases of hyperthyroidism with cardiac symptoms. The other groups are similar to the corresponding groups in Chart 1.

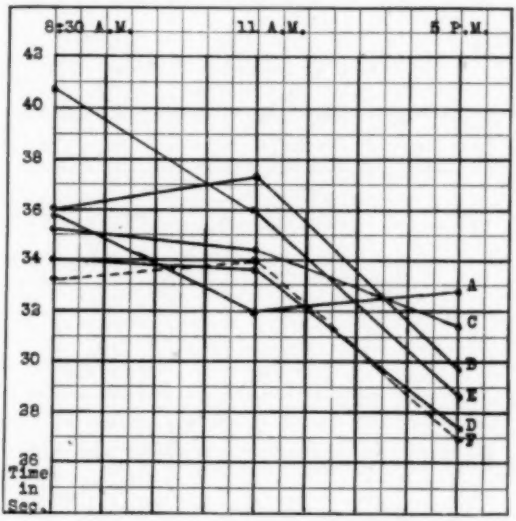

Chart 1.—Day curve of vasomotor reflex. A, physically inferior, eight cases; B, constitutionally inferior, seven cases; C, post-infection, twelve cases; D, organic, eighteen cases; E, emotionally sensitive, four cases; F, neurotic, five cases. Above are charted the average morning, midday and evening readings of the reflex of various groups of patients.

It will be seen from the chart that the two larger groups—the groups of the physically inferior and the constitutionally inferior—show definite fatigue of almost equal degree. Of sixteen men in these two classes, thirteen complained of fatigue from these light "setting-up" exercises. To avoid prejudice on the part of the observer, the readings were made before the men were interrogated as to their symptoms. It is, therefore, evident that patients belonging to either of these two groups do not imagine their fatigue; it has, apparently, a physical basis. From the general attitude of these men, one is

9. Lee, F. S.: Pop. Science Monthly, February, 1910.

rather apt to feel that, as suggested by Lee,[9] fatigue has "become a habit" with them. He says, "Our sensations become our servants or our masters, according as we will." There is no doubt that men of these classes are servants of their sensations, and that fatigue has

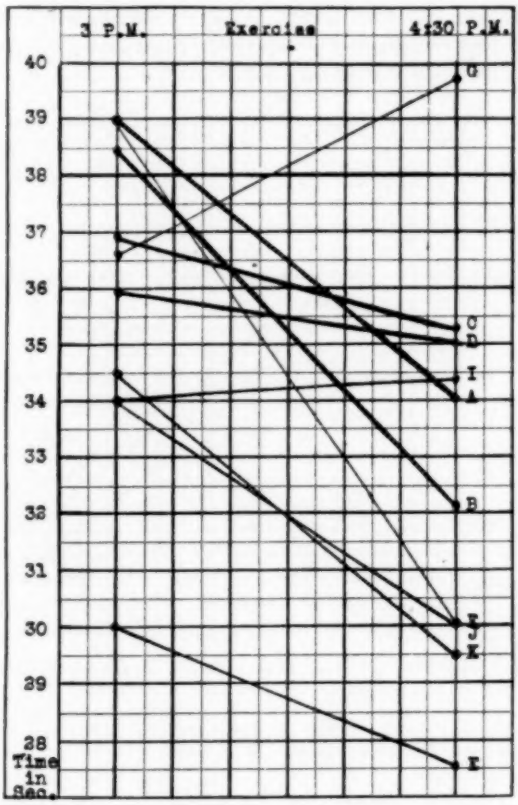

Chart 2.—Vasomotor reflex before and after exercise. A, physically inferior, five cases; B, constitutionally inferior, eleven cases; C, post-infection, ten cases; D, organic, fourteen cases; E, neurologic, two cases F, emotionally sensitive, one case; G, chronic invalidism, three cases; I, neurotic, three cases; J, no disease, one case; K, hyperthyroidism, two cases.

become a habit, but it is illuminating to see that they actually suffer more fatigue than do their fellows of the organic and post-infection groups. The records of the smaller groups require no comment, except to point out that, here again, the emotionally sensitive group, as was the case in the day curve (Chart 1), shows the most marked

fatigue. Group G shows the "duration time" increased after exercise. Such a phenomenon is not uncommon in individuals who are physically strong. In this case the average reading after exercise was carried up by one that was nine seconds longer after exercise than before. The subject who showed this was an unusually powerful and active man; his symptoms were of purely psychoneurotic nature.

The organic and post-infection groups are much alike. The organic group may be considered a fairly satisfactory normal control, so far as fatigue is concerned, on the functional groups. All the men in the organic group had mild cardiac lesions well compensated. There was a striking correspondence between the sensations of these men and the readings of the vasomotor reflex. In the case of five men who did not complain of fatigue there was an average prolongation of the "duration time" of three seconds; eight men who complained of varying degrees of fatigue showed an average shortening of the time by three and one-half seconds. The neurologic group contains patients with irritable heart who have definite history or signs of organic neurologic disease, such as epilepsy. The group of the chronic invalids consists of men with the same symptoms as have all the other functional cardiac cases and who are chronic psychoneurotic patients with a history of chronic invalidism. The neurotic group contains men with the same symptoms, with somatic nervous phenomena, such as vomiting, frequent fainting, or excessive giddiness.

Why so many men with irritable heart have rapid fatigue is a problem which defies solution without further data. Lee[9] says that "physical training . . . consists largely in the development of a power of resistance to the toxic fatigue substance." These men have not exercised in the past (most of them), and they have very little resistance to fatigue. The development of such resistance is probably not the least of the benefits which patients with irritable heart derive from graded exercises.

The Vasomotor Reflex and the Skeletal Musculature.—After the day curve of the vasomotor reflex had been observed in sixty-five men, it was thought that a comparison of these figures with the total muscle strength of the same men might prove of interest. This was done without regard to the nature of their various disabilities. The vasomotor reflex time was calculated by taking the average "duration time" of the three readings—morning, noon and evening. These figures are compared in Chart 3 with the strength to weight ratio of the same men. This ratio had been determined by Captain Bertnard Smith and the writer. It was done by first estimating the total body strength by use of the Martin spring balance, and then dividing this figure by the weight of the individual. The resulting ratio represents

the total muscular efficiency of the individual. In Chart 3 the vasomotor reflex readings are arranged in sequence, from the longest "duration time" (46 seconds) to the shortest (20 seconds). The strength-weight ratio is indicated by the same scale. There is a general but definite relation between the "duration time" and the strength-weight ratio. The men with vasomotor reflex times of relatively long duration are the stronger men. This would seem to indicate that

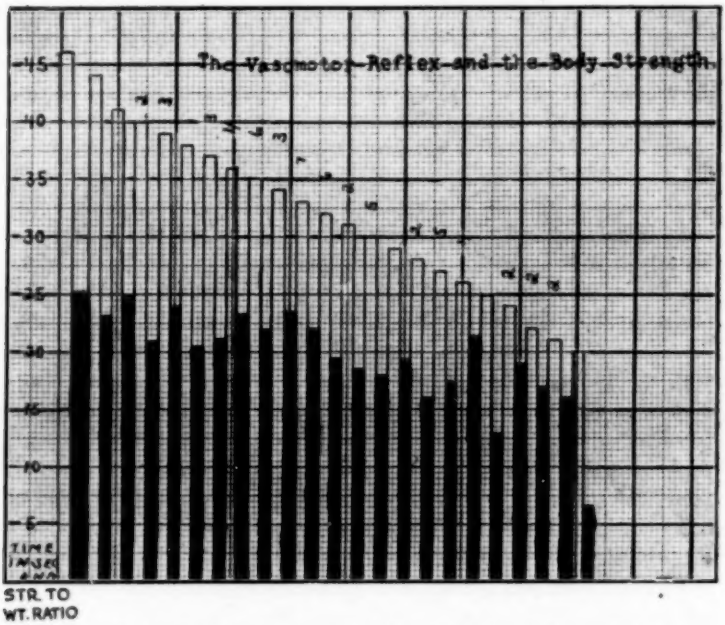

Chart 3.—The hollow blocks represent the vasomotor reflex, and the numbers over the columns indicate the number of men whose "duration time" is thus shown. The solid columns represent the strength-weight ratios of the same men grouped in the same order.

there is a correspondence between the strength of the arteriolar musculature and the skeletal musculature in a given individual.

The Convalescent Curve.—During the influenza epidemic the day curve of the vasomotor reflex was observed in the case of seven men, all of whom were in the first week of convalescence from uncomplicated influenza. These men had not yet returned to graded exercises or to educational work, although they were up and about their rooms. The curves are shown in Chart 4. The type of curve is characteristic and is unlike any of the normal day curves. This V-shaped curve is

uniformly present in the seven patients tested, except in the case marked 1 on the chart: this patient had the most severe illness of any and was out of bed for the first time. This probably accounts for the fact that he did not show recovery from fatigue in the afternoon, such as is shown by all the others. This rise in the "duration time" during the afternoon in the other men is difficult to explain. The morning seems to have caused fatigue in each case. The only difference

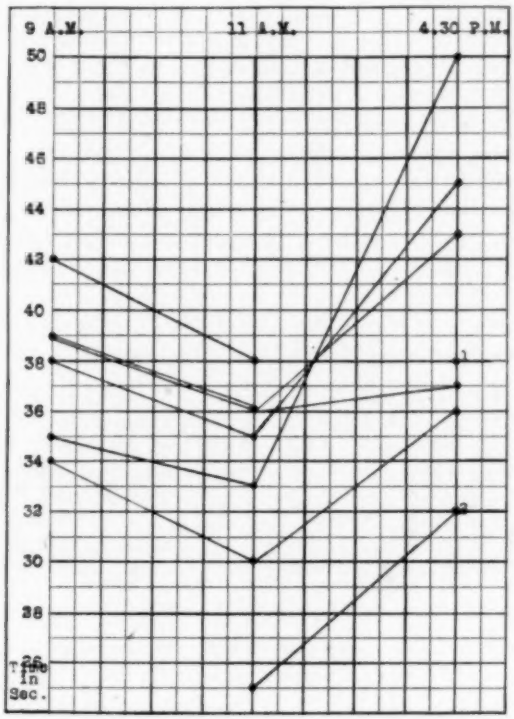

Chart 4.—Day curve in patients convalescent from influenza.

between the morning and afternoon routine of these men consisted in cleaning their rooms in the mornings, while the afternoons were devoted to absolute rest. Further observations on patients convalescent in bed should be made, as such a study might produce a method of determining the end of convalescence.

This work was done under the direction of Major Francis W. Peabody in the general study of the Irritable Heart of Soldiers at U. S. A. General Hospital 9, Lakewood, N. J.

CONCLUSIONS

1. The quantitative estimation of fatigue by the white vasomotor reaction, as suggested by Ryan, is of value in the study of clinical conditions. Owing to the various sources of possible error in the test, it is more suitable for group study than for individual cases.

2. The day curve of fatigue estimations is much the same in the several groups of cases that have the syndrome of irritable heart as in those with organic heart disease.

3. Patients with irritable heart who fall into the groups of general constitutional inferiority or pure physical inferiority show very rapid fatigue on exercise. This fatigue can be measured, and is an actual physical phenomenon and not of psychic origin.

4. There is a correspondence between the general body strength and the duration of the white vasomotor reflex. This suggests that there is a relationship between the strength of the skeletal musculature and the arteriolar musculature in a given individual. It is not considered, however, that the test is accurate enough to warrant estimating body strength from the vasomotor reflex in an individual case.

5. An unusual type of day fatigue curve, of V-shape, is usually found in patients convalescent from influenza. It is unlike the day curve obtained in any ambulant patient and may be characteristic of convalescence.

INFORMATION FOR AUTHORS OF MILITARY MEDICAL PAPERS

The circular on Medical Publications issued by the Surgeon-General's Office, March 27 and May 22, 1918, required (Paragraph 423, Manual of the Medical Department) that all medical manuscripts by medical officers, U. S. Army, intended for publication should be first submitted for approval to the Surgeon-General's Office, Washington, D. C. This regulation is still in force as far as medical officers on active duty are concerned. In the case of medical officers recently retired from active duty, in S. G. O. 700.7, issued March 20, 1919, it is requested, as a courtesy to the Surgeon-General and in aid of assembling material for the Medical History of the War, that all medical manuscripts based on military or official records or on military experience during the war, be submitted for record and approval, as heretofore, to the Secretary, Board of Publications, Surgeon-General's Office, Washington, D. C., and that such manuscript be accompanied by a carbon copy. On approval, the original copy will be forwarded for publication to the journal designated, and the carbon will be filed in the records of the Medical History of the War.